Nutrition in Pancreatic Diseases

Topic 14

Module 14.1

Nutritional Support in Acute Pancreatitis

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Learning Objectives

- To learn how to discriminate between patients with mild or severe pancreatitis;
- To appreciate the impact of adequate nutritional support on clinical outcome in patients with acute pancreatitis;
- To learn about the benefits and the risks of enteral and parenteral nutrition in patients with acute pancreatitis;
- To learn the best approach to nutritional support in patients with severe and complicated acute pancreatitis.

Contents

Key Messages

- Both severity of acute pancreatitis and the patient's nutritional status predict outcome, therefore both have to be assessed;
- Adequate nutritional support is crucial in patients with severe and complicated pancreatitis. Negative energy balance has an adverse impact on nutritional status, the disease progression, and outcome;
- In mild pancreatitis, neither enteral nor parenteral nutrition have any positive impact on the course of the disease if the patient can start to eat within five to seven days. Therefore, no specific nutritional support is recommended in this situation;
- If oral nutrition is not possible due to consistent pain for more than five to seven days, enteral tube feeding should be started;

- Early enteral nutrition improves the course of severe pancreatitis. Continuous enteral jejunal nutrition is therefore recommended in all patients who tolerate it. If nutritional requirements cannot be met via the enteral route supplementary parenteral nutrition should be given;
- In case of surgery for pancreatitis, intraoperative insertion of a fine needle jejunostomy for postoperative feeding should be considered;
- Early enteral nutrition with a jejunal tube is well tolerated and safe in patients with acute severe pancreatitis. Endoscopic tube placement is easy to perform;
- Whether nasogastric feeding is an adequate alternative to jejunal feeding is unclear from present data;
- Continuous jejunal administration with a peptide-based formula is safe and effective and is currently the method of choice. Standard or immune-enhancing formulae can be tried if they are tolerated.

1. Introduction

Acute pancreatitis occurs in different clinical patterns ranging from a mild to a severe necrotizing disease with local and systemic complications. Acute pancreatitis involves a systemic immuno-inflammatory response to a localized process of autodigestion of the pancreatic gland, with variable involvement of the peri-pancreatic tissue and remote organ systems.

Alcohol abuse in men and gallstone disease in women are the most common causes of acute pancreatitis. The mechanisms by which these factors cause acute pancreatitis are still not clearly understood.
The major pathological processes in acute pancreatitis are inflammation, oedema, and necrosis of the pancreatic tissue as well as inflammation and injury of extrapancreatic organs (1).

75-80% of patients have mild, oedematous and about 20-25% severe necrotizing pancreatitis.
The mortality rate for mild to moderate pancreatitis is low (1%). The mortality rate in severe pancreatitis increases to 19-30% (2). Mortality approaches 50% if necrosis of the gland is greater 50% and can further increase up to 80% if sepsis occurs (3). Approximately half of the deaths in acute pancreatitis occur within the first two weeks of illness and are mainly attributable to organ failure. The other 50% of deaths occur weeks to months after this period, and are related to organ failure associated with infected necrosis.

Nutritional support in severe necrotising pancreatitis is essential because these patients rapidly develop nutritional deficiencies. This is even more likely to be fatal if patients are already malnourished at the time of the initial attack.

2. Outcome predictors

Two factors, (a) the severity of pancreatitis and (b) nutritional status can be used to predict the outcome in acute pancreatitis.

2.1 Assessment of the severity of the acute pancreatitis

Several prognostic scoring systems, which include clinical (Ranson-Score, Glasgow-Score, APACHE II-Score, Atlanta Classification), laboratory, and radiological criteria are available (4-7). The Atlanta Classification of severity defines severe acute pancreatitis on the basis of standard clinical manifestations: a score of 3 or more in the Ranson Criteria (Table 1) (6), a score of 8 or more in the APACHE II-Score, evidence of organ failure and the intrapancreatic pathological findings (necrosis or interstitial pancreatitis). This classification is helpful because it also allows comparison of different trials and methodologies. The severity of acute pancreatitis based on imaging procedures is based on the Balthazar-Score, which predicts severity on CT appearance, including presence or absence of necrosis (Table 2) (7). Failure of pancreatic parenchyma to enhance during the arterial phase of intravenous contrast-enhanced CT indicates necrosis, which predicts a severe attack if more than 50% of the gland is affected. The measurement of concentrations of serum C-reactive protein (CRP) is very useful in clinical practice. CRP concentration has an independent prognostic value. A peak of more than 210 mg/l on day 2 to 4, or more than 120 mg/l at the end of the first week, is as predictive as multiple-factor scoring systems (8).

Table 1 Ranson's criteria for severity of acute pancreatitis (6)

Admission criteria Age > 55 years WBC > $16.0x10^9$/L Gucose > 10 mmol/l Lactate dehydrogenase (LDH) > 350 IU/L Aspartamine Transaminase (AST) >250 U/L
Following initial 48 hours Criteria Hematocrit decrease of >10% BUN increase of > 1.8 mmol/l Calcium < 2 mmol/l PaO_2 < 60 mmHg Base deficit > 4 mEq/L Fluid sequestration >6 L

Table 2 Computed tomography (CT) grading system of Balthazar (7)

CT grade		**Quantity of necrotic pancreas**
Grade A = **0**	Normal pancreas	
Grade B = **1**	Focal or diffuse enlargement of the pancreas	
Grade C = **2**	Pancreatic gland abnormalities accompanied by mild parapancreatic inflammatory changes	< 33% = **2** 33% - 50% = **4**
Grade D = **3**	Fluid collection in a single location, usually within the anterior pararenal space	> 50% = **6**
Grade E = **4**	Two or more fluid collections near the pancreas or gas either within the pancreas or within parapancreatic inflammation	
Total score = CT grade (0-4) + necrosis (0-6)		

2.2 Nutritional status

Both undernutrition and overweight are seen commonly in patients with acute pancreatitis. Both are well-known risk factors for more complications and higher mortality. Undernutrition is known to occur in 50-80% of chronic alcoholics and alcohol is a major aetiological factor in acute pancreatitis patients (30-40%) (9).

To plan appropriate nutritional support it is therefore necessary to assess both the severity of acute pancreatitis and the nutritional status at the time of admission and during the course of the disease.

3. Energy and substrate metabolism during acute pancreatitis

Specific and non-specific metabolic changes occur during acute pancreatitis. A variety of proinflammatory cytokines raise the basal metabolic rate, thereby increasing energy consumption. The resting energy expenditure varies according to the severity and the length of disease. If patients develop sepsis, 80% of them show an elevation in protein catabolism and an increased nutrient requirement. A prolonged negative nitrogen balance is associated with worse clinical outcome (10), although whether this is a direct

or indirect effect is unclear. Severe protein catabolism may simply be a reflection of the severity of the underlying disease, which is itself the major determinant of outcome. There is no nutritional study available in which patients were stratified according to the disease severity.

3.1 Metabolism of carbohydrates

Glucose metabolism in acute pancreatitis is determined by an increase in energy demand as well as any chronic damage to the islets of Langerhans. Endogenous gluconeogenesis is increased as a consequence of the metabolic response to the severe inflammatory process. Exogenous glucose is an important source of energy but, unlike the normal response in health, it can only partially counteract the rise in gluconeogenesis from protein degradation resulting from the response to injury. Protein sparing is therefore only partial (11). The maximum rate of glucose oxidation is approximately 4 mg/kg/min and, therefore, administration of glucose at rates in excess of this can be harmful, and even wasteful, since it merely increases oxygen consumption and CO2 production as well as increasing lipogenesis and glucose recycling. Increasing demand for gas exchange may be disastrous in the presence of respiratory failure e.g. from ARDS. High rates of glucose infusion also cause hyperglycaemia, a major risk factor for infectious and metabolic complications. Monitoring of blood glucose and controlling its level, if necessary by insulin infusion, is therefore essential.

3.2 Protein metabolism

A negative nitrogen balance is often seen in severe acute pancreatitis and may, correlate with an adverse clinical outcome if protein losses are large. These can be as high as 20-40 g/day in severe cases. These protein losses must be minimized and the increased protein turnover must be compensated as far as possible. If acute pancreatitis is complicated by sepsis, up to 80% of the patients are in a hypermetabolic state with a significant increase in resting energy expenditure. The strategy should therefore be to minimize the catabolic stress, e.g. by aggressive treatment of infection, fluid loss and pain, and by optimising nutritional support, giving adequate amounts of both energy and protein. Even then, some loss of lean mass is inevitable in response to inflammation and immobility. Nonetheless by good clinical and nutritional management the damage can be reduced and outcome improved.

3.3 Lipid metabolism

Hyperlipidaemia is a common finding in acute pancreatitis. The mechanism of altered lipid metabolism is not entirely clear. After an acute attack, serum lipid concentration returns to normal ranges. It is also known that in some patients severe hyperlipidaemia itself can cause acute pancreatitis (12).

4. Exocrine pancreatic stimulation by macronutrients

Although the administration of glucose, protein and fat are necessary, for a long time it was considered that enteral feeding was harmful because of the potential stimulation of exocrine pancreatic enzyme secretions.

However studies have shown that glucose infusion into the jejunum is only a very weak stimulus for exocrine pancreatic secretory response and that jejunal infusion of elemental diets containing defined amounts of protein or amino acids are well tolerated and do not stimulate exocrine pancreatic secretion (13, 14). Stimulation of exocrine pancreatic secretion by enteral administration of lipids depends on the anatomical site of administration. If the lipids are given into the proximal jejunum, there is only a minimal stimulation of exocrine pancreatic secretion.

The intravenous infusion of macronutrients with regard to exocrine pancreatic stimulation is safe (15, 16). The administration of glucose intravenously does not stimulate the exocrine pancreatic secretion, the main risk of intravenous glucose in acute pancreatitis being hyperglycemia due to the insulin resistance which occurs in critically ill patients. Intravenous administrations of protein hydrolysates have resulted in either an inhibition of exocrine secretory responses or no effect. Pancreatic exocrine secretion is not stimulated by intravenous lipids.

All these findings have changed our concepts of nutritional management in acute pancreatitis. Nowadays, enteral feeding via the jejunum is regarded as safe since it is associated with negligible stimulus to the pancreas and no worsening of the autodigestive processes in and around the pancreas. It may also help in maintaining gut integrity by modulating the GI-tract associated systemic immunity.

5. Energy requirements

As described above, patients with severe acute pancreatitis are hypermetabolic in proportion to the severity of their disease. Resting energy expenditure can be variable and has been reported as 77-158% of the predicted energy expenditure (17). Complications such as sepsis or multiorgan failure further exacerbate the catabolic state and the rise in resting energy expenditure.

It was shown that, in severe acute pancreatitis, the Harris-Benedict equation is not sensitive enough to estimate the caloric expenditure with any accuracy. In these cases, indirect calorimetry, if available, is recommended in order to avoid over- or underfeeding.

For both enteral and parenteral nutrition, an energy intake of 25-35kcal/kgBW/d is recommended. Overfeeding and hyperglycemia should be avoided (see above). Recommended carbohydrate intake is 3-6 g/kgBW/day but blood glucose concentration should not be allowed to exceed 10 mmol/l. Insulin treatment is recommended at a maximum rate of 4-6 units per hour. Even then the glucose oxidation rate remains subnormal.

A protein intake of 1.2 to 1.5g/kgBW/d is optimal with no benefit to nitrogen balance at higher rates which merely increase the urea production rate. Lower protein intakes cause less than optimal nitrogen balance and should only be considered in those few patients with severe renal or hepatic failure.

Fat can be given up to 2g/kgBW/d, but blood triglyceride levels must be monitored carefully. Triglycerides are tolerated up to 12 mmol/l.

6. Enteral or parenteral nutrition

Total parenteral Nutrition (TPN) was used in the past to avoid stimulation of exocrine pancreatic secretion. Several prospective, randomized clinical trials have been performed comparing enteral with parenteral nutrition in patients with acute pancreatitis (18-24). In mild to moderate acute pancreatitis these studies showed no beneficial effect of either treatment on outcome in these patients (18, 19). TPN did not change the course of the disease but was more expensive or accompanied by an increase in catheter-related infections and a longer hospital stay. It has become clear, that these complications were often the consequence of overfeeding. Van den Berghe et al. showed, irrespective of the route of nutritional support that the control of hyperglycemia with insulin reduced mortality in critical care patients (25). Recently, the emphasis of nutritional management in acute pancreatitis has shifted from parenteral to enteral feeding. Enteral feeding reduces net catabolism and loss of lean mass, and it may also modulate the acute phase response, preserving visceral protein metabolism and possibly down-regulating the splanchnic cytokine response (26) (Table 3).

Table 3 Benefits of early enteral feeding

Maintain gut integrity (reduce bacterial challenge)
Set tone for systemic immunity (down-regulate immune response)
Attenuate oxidative stress
Lessen disease severity
Promote faster resolution of disease process
Reduce complications (less infection and need for surgical intervention, shorter hospital length of stay, and possibly less multiple organ failure)

In the studies comparing enteral with parenteral nutrition in acute pancreatitis, the results differed between, on the one hand, severe and, on the other, mild to moderate pancreatitis. In the first prospective study by Kalferanzos et al compared a semi-elemental feed given via a naso-jejunal tube with TPN started 48 hours after admission and showed that enteral feeding was well tolerated without adverse effects. In addition, the patients on enteral nutrition experienced fewer septic complications and fewer total complications compared to those receiving parenteral nutrition. Furthermore, the costs of nutritional support were three times higher in patients receiving TPN (20). These findings are supported by

several other studies (21-24). The study of Windsor et al (21) showed that enteral nutrition attenuates the acute phase response in acute pancreatitis and improves disease severity and clinical outcome, despite the fact that pancreatic injuries were virtually unchanged on CT-scan. In the enteral feeding group, SIRS and sepsis were reduced, resulting in a beneficial clinical outcome (APACHE II-score and C-reactive protein). Abou-Assi et al treated 156 patients with acute pancreatitis initially with i.v. fluid and analgesics. Those who improved rapidly were fed orally afterwards. The non-responders were randomized to receive either enteral nutrition by a naso-jejunal tube or TPN. 75% of the initially enrolled patients improved with the oral regimen and were discharged within four days. Those randomized to the enteral group were fed for a significantly shorter period (6.7 days vs. 10.8 days) and had significantly fewer metabolic and septic complications. In addition, hyperglycemia, requiring insulin therapy, was significantly more frequent in the parenterally fed patients (22). Petrov et al randomized 70 patients out of 466 patients with acute pancreatitis to enteral or parenteral nutrition. They showed again that enteral nutrition was superior to parenteral nutrition by decreasing complications, single and multiorgan failure and mortality (24).

Today, there is no doubt, that enteral nutrition should be tried first in patients with severe acute pancreatitis. The meta-analysis from McClave et al (27) showed that, when compared with PN, EN was associated with a significant reduction in morbidity from infection, a reduction in length of hospital stay and a trend toward reduced organ failure. There was no overall difference in mortality.

7. Nutritional support in mild to moderate pancreatitis

There is no evidence that nutritional support (enteral or parenteral) has a beneficial effect on clinical outcome in patients with mild acute pancreatitis (28). Enteral nutrition is unnecessary, if the patients can consume normal food after 5 to 7 days (ESPEN Guidelines: Grade B).

Enteral or parenteral nutrition within 5 to 7 days has no positive effect on the course of the disease and is therefore not recommended (ESPEN Guidelines: Grade A). Early enteral nutrition support can be of importance in patients with pre-existing severe malnutrition or in patients when resumption of oral feeding in 5 to 7 days is not possible. Figure 1 shows a frequently used approach for these patients.

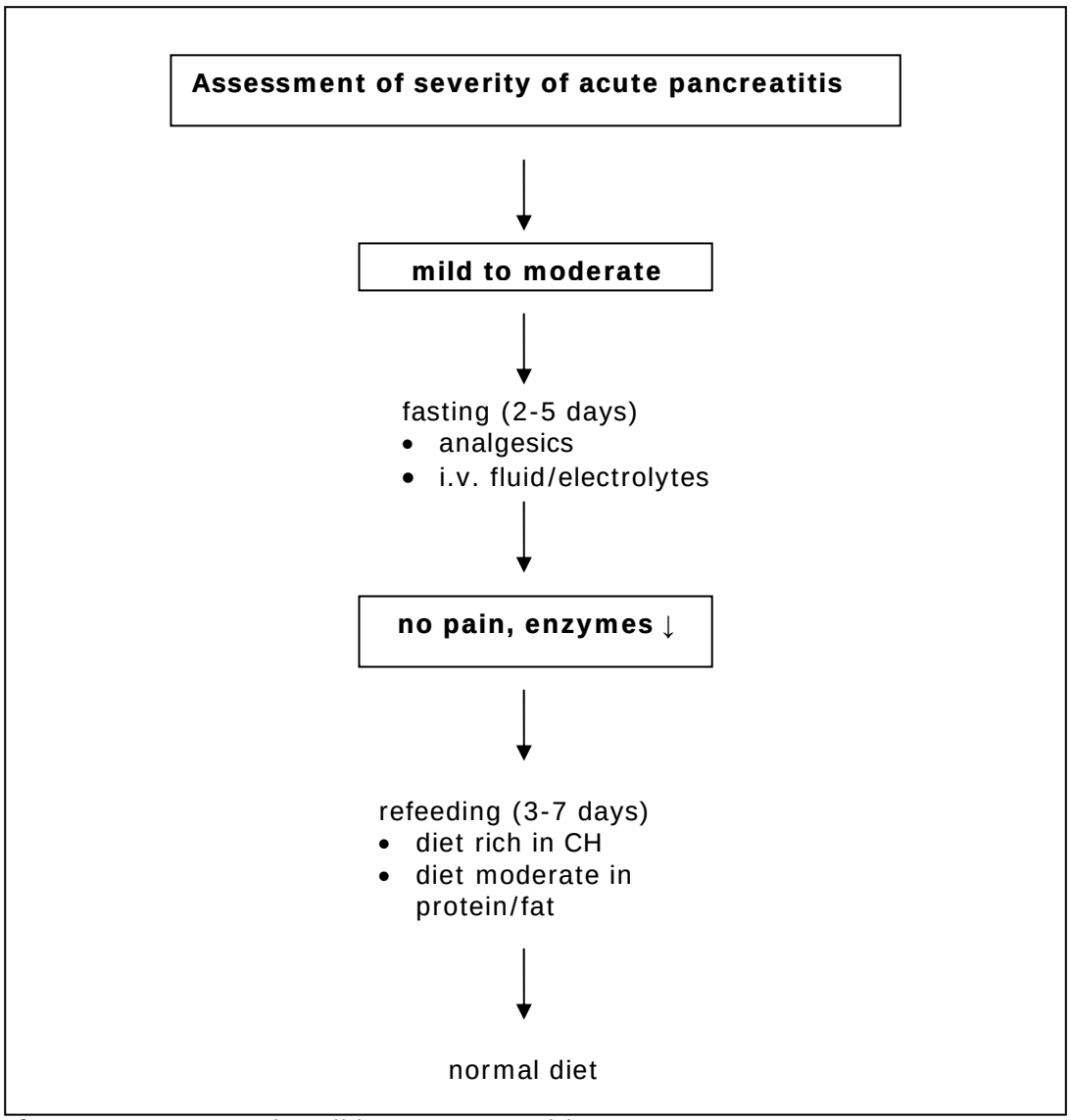

Figure 1 Management for mild acute pancreatitis

8. Nutritional support in severe acute pancreatitis

In patients with severe pancreatitis, who have complications or need surgery, early nutritional support is necessary to prevent the adverse effect of nutrient deprivation. In severe necrotizing pancreatitis, enteral nutrition is indicated first if possible (ESPEN Guidelines: Grade A) (28) as it has been shown in many studies to be safe, effective, and well tolerated. As discussed above, EN is superior to PN, although, if EN is insufficiently tolerated, it may be necessary to supplement with PN, at least for a time, in order to reach nutritional goals. The administration of fat in parenteral nutrition can be regarded as safe, if hypertriglyceridemia (<12 µmol/l) is avoided (28). A practical approach to nutrition in severe acute pancreatitis is outlined in Figure 2.

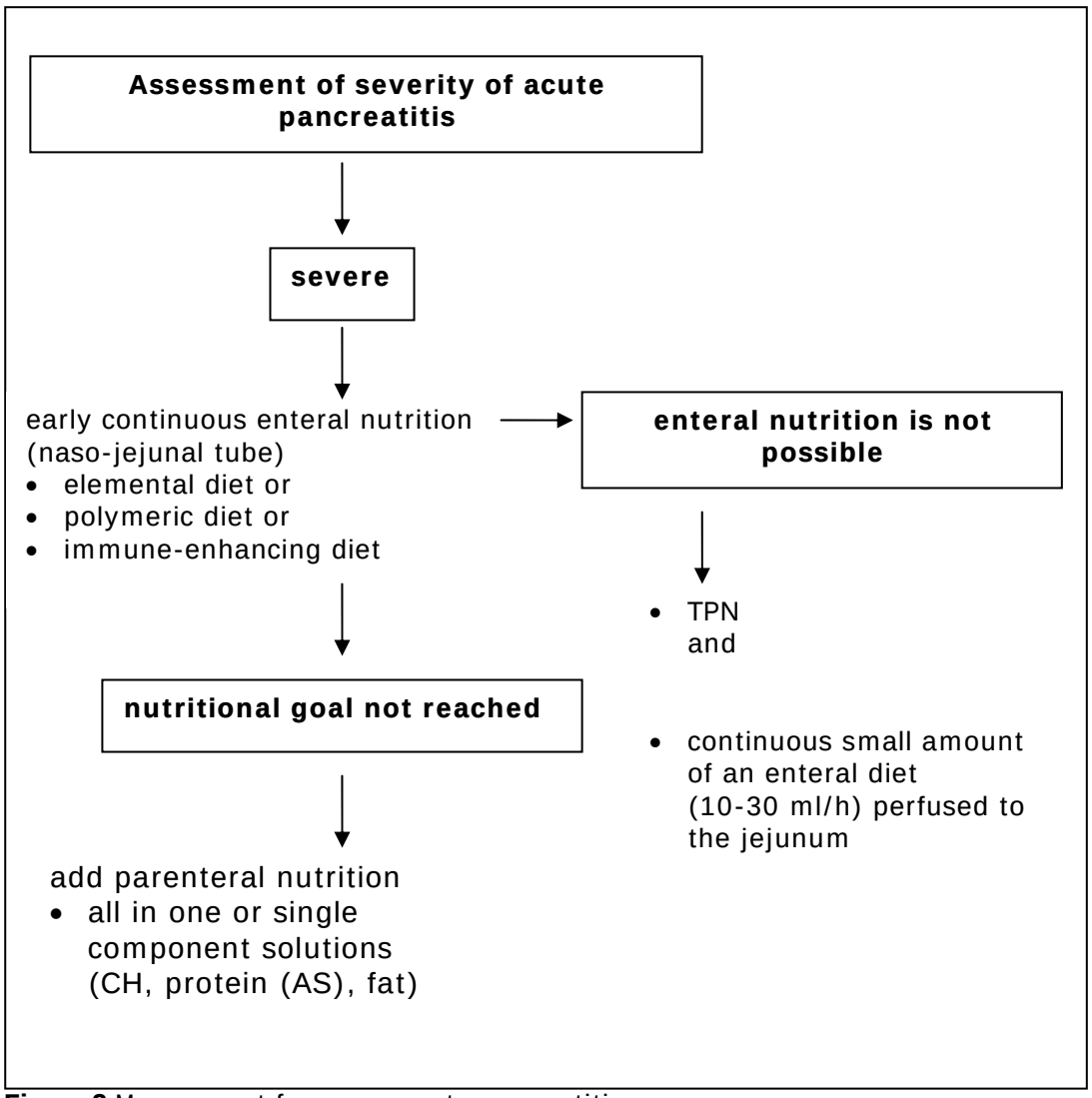

Figure 2 Management for severe acute pancreatitis

8.1 Route of feeding

The route of nutrient delivery (parenteral/enteral) should be determined by patients' tolerance. Tube feeding is possible in the majority of patients, but, as described above, some patients need supplementation with parenteral nutrition (ESPEN Guideline: Grade A). Several prospective studies have shown that jejunal tube feeding is possible in most patients with acute pancreatitis (28). Placing a jejunal feeding tube distal to the ligament of Treitz is relatively easy either under fluoroscopic control or more often endoscopically. Normally, jejunal tubes are well tolerated (19, 29-31). Rarely, proximal migration of the feeding tube and subsequent pancreatic stimulation can aggravate acute pancreatitis (32). Partial ileus is not a contraindication to enteral feeding because patients with this condition usually tolerate continuous low-rate infusion of nutrients. Several types of single or multi-lumen tubes are available (Fig. 3). In those undergoing surgery for pancreatitis, placement of a needle catheter jejunostomy intra-operatively, is useful (Fig. 4).

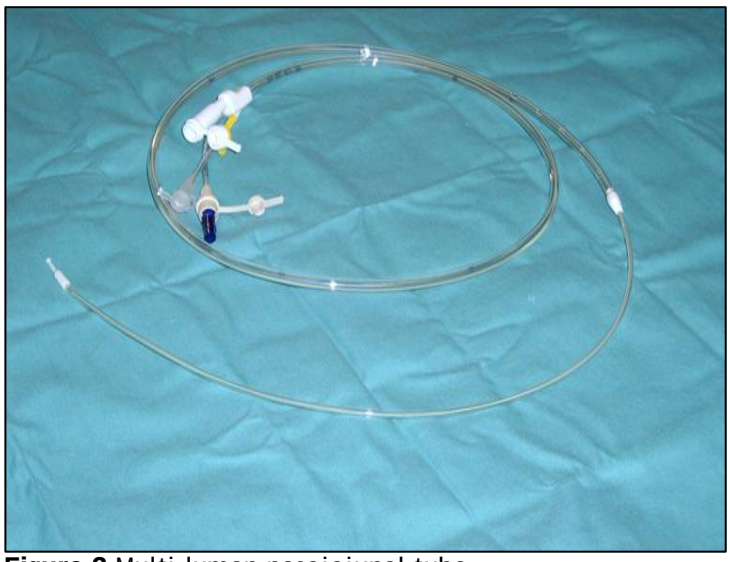

Figure 3 Multi-lumen nasojejunal tube

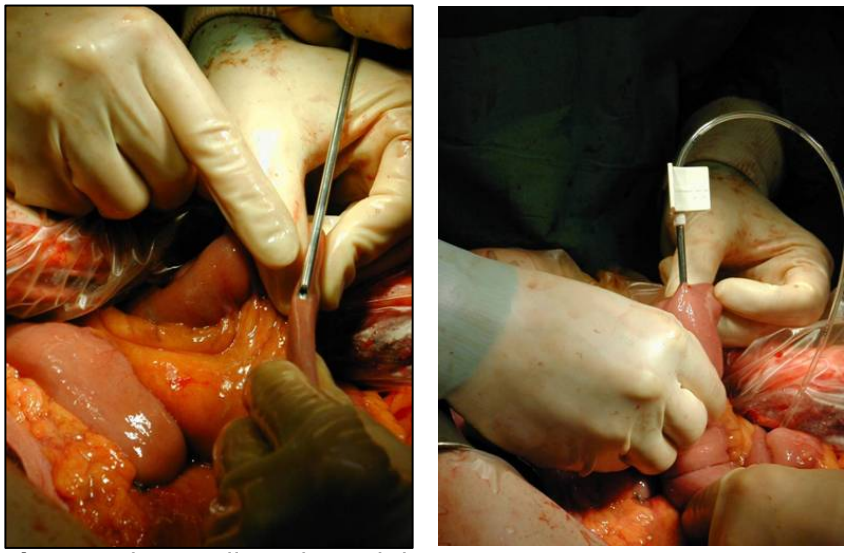

Figure 4 Fine needle catheter-jejunostomy

8.2 Which formula should be used in acute pancreatitis?

Most studies have been done using peptide-based formulae which have shown beneficial effects (ESPEN Guidelines: Grade A) (28). In most institutions polymeric formulae are now used. A direct comparison of a peptide-based and a polymeric formula showed that there was no difference on outcome (34). Today, it is common to start with a standard polymeric formula and, if this is not tolerated, a peptide-based formula is tried. Several published trials have also used formulae containing immune modulating substrates (glutamine, arginine, n-3 polyunsaturated fatty acids) or pre- and probiotics (27). These formulae cannot be generally recommended because the studies concerned involved too small numbers of patients and require confirmation in larger trials. The concept of using pre- and probiotics to prevent intestinal bacterial translocation is very attractive and preliminary data have shown beneficial effects (35).

Several studies of TPN supplemented with glutamine have also demonstrated beneficial effects (27).

8.3 Nasogastric versus jejunal feeding

Whether feeding via the jejunum is absolutely necessary is not clear. The aim of minimizing stimulation of the exocrine pancreatic secretion would support the jejunal feeding route but whether this is of any importance in terms of outcome is unclear. Recently, two randomized studies comparing naso-gastric versus naso-jeunal feeding in severe acute pancreatitis were published (36, 37). In these studies, naso-gastric feeding was as safe as naso-jejunal feeding; little difference was documented between the two methods with respect to pain, analgesic requirements, serum CRP concentration, or clinical outcome, but again, no clear recommendation can be made. If a multilumen tube is used, it is possible to first try

feeding through the gastric port, and, if this is not tolerated, then switch to the jejunal port. More clinical trials are needed to address these issues.

9. Oral refeeding

There are limited data available on oral refeeding. Oral feeding with normal food and/or oral supplements can be progressively attempted once gastric outlet obstruction has resolved, provided it does not result in pain, and if complications are under control. Tube feeding can be gradually withdrawn as intake improves. Currently, there are only two studies investigating oral refeeding (38, 39). In the study of Levy et al 21% of patients experienced a pain relapse on the first and second day of refeeding. Serum lipase concentration > 3 x the upper limit of the normal range and higher Balthazar's CT-scores at the onset of refeeding were identified as risk factors for pain relapse (38).

10. Nutritional support in patients after pancreatic surgery

Postoperative feeding with a needle catheter jejunostomy was successful in several small studies (30, 33, 40). Hernandez-Aranda et al found no difference between groups of patients who received postoperative parenteral nutrition or enteral nutrition via a jejunostomy (40). Furthermore, in patients undergoing surgery for severe acute pancreatitis, needle catheter jejunostomy for longterm enteral nutrition was used safely and with no nutritional risk (33). In these patients, nutritional support has to be planned before the operation, according to the clinical situation and the course of the disease.

11. Summary

75-80% of patients with acute pancreatitis has mild to moderate disease and do not need specific nutritional support. Early oral refeeding can be started within a few days if the patients have no pain or GI-disturbances. There is no evidence that enteral tube feeding or parenteral nutrition is of benefit in these patients. There are no data available to give a nutritional recommendation in patients with severe pre-existing malnutrition but such patients should be managed in the same manner as any other patient suffering malnutrition.

Patients with severe disease, complications or the need for surgery require early nutritional support. In patients with severe pancreatitis, enteral feeding by the jejunal route should be established as soon as possible, but supplemented with parenteral nutrition if it is impossible to reach target intakes by the enteral route alone. For the future, several questions need addressing; the optimal timing of nutritional therapy; the optimal feeding site (oral, gastric, jejunal or TPN); the optimal nutrient formulation, i.e. semi-elemental, polymeric immune-enhancing, pre- and probiotics. Furthermore, in any future studies there needs to be a clear stratification of the patients according to their disease severity and their nutritional status on admission.

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