Nutritional Support in Pancreatic Disease Topic 14

Module 14.1

Nutrition in Acute Pancreatitis

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Learning Objectives

- To learn how to discriminate 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

- Severity of acute pancreatitis and nutritional status predict outcome, therefore both have to be assessed in these patients;
- Adequate nutritional support is crucial in patients with severe and complicated pancreatitis. In severe acute pancreatitis a negative energy balance has a negative impact on the nutritional status and the disease progression;

- In mild pancreatitis, enteral or parenteral nutrition has no positive impact on the course of the disease if the patient can start to eat early and is on a full diet within five to seven days. Therefore, no specific nutritional support is recommended;
- In severe acute pancreatitis early nutritional support is essential;
- Not all patients need nutritional support by a tube, some tolerate oral nutrition;
- If oral nutrition is not possible due to consistent pain for more than five to seven days, enteral nutrition should be started without delay;
- Gastric feeding is an acceptable and safe alternative to jejunal feeding in the absence of intolerance;
- 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;
- Continuous gastric or jejunal administration of a standard formula is usually tried first today, and continued if they are tolerated. Peptide-based formulae can be recommended if there is intolerance to the polymeric formula. They are safe and also proven to be effective;
- Early enteral nutrition improves the course of severe pancreatitis. Continuous enteral gastric or jejunal nutrition is therefore recommended in all patients according to the tolerance. If the caloric goal cannot be reached with enteral nutrition, parenteral nutrition should be added;
- When parenteral nutrition is given, overfeeding should be avoided;
- In parenteral nutrition glutamine and n-3 fatty acid administration can be considered;
- Surgery for complications of acute pancreas provides an important opportunity to obtain enteral access, either by needle catheter jejunostomy or nasojejunal feeding tube.

1. Introduction

Acute pancreatitis occurs in different clinical patterns ranging from a mild and mostly self-limiting form to severe necrotizing disease with local and systemic complications (1). 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 important underlying conditions for acute pancreatitis.
The sentinel acute pancreatitis event (SAPE) hypothesis suggests that while there is a plethora of aetiological agents or insults, which may injure the pancreas, there is a final common pathway of inflammation in the disease process termed the "sentinel event". The acute insult, which initiates the event, can vary from a gallstone to a drug to alcohol. The sentinel event, however, refers to the subsequent vicious cycle of inflammation. An early pro-inflammatory process starts with the stimulation of chemotaxis and migration of neutrophils into and around the pancreatic acinus, with neutrophil activation, recruitment, and infiltration. This is followed by a later pro-fibrotic response that involves stimulation of stellate cells surrounding the acinar cells. It is not the initial insult, but the subsequent sentinel event and its vicious cycle of inflammation that drives the morbidity and mortality.
As the sentinel event sets up around the acinar cell, two defects occur which promote further inflammation and stimulate autolysis or autodigestion of the pancreatic tissue. The first defect is an intra-acinar activation of pancreatic enzymes in which zymogen are co-localized with lysosomal enzymes like cathepsin. The second defect is inhibition of secretion, in which the zymogen enzymes are activated, but then retained within the acinar cell (2).
This process results in inflammation, oedema, and necrosis of the pancreatic tissue as well as inflammation and injury of extrapancreatic organs (3).
Acute pancreatitis can be mild (absence of local complications or organ failure) or severe (persistent organ failure). 75-80% of patients have mild, oedematous disease, and about 20-25% severe necrotizing pancreatitis.

The mortality rate for mild to moderate pancreatitis is low (<1%). Up to 80% will tolerate an oral diet within 7 days. The mortality rate for severe pancreatitis increases to 19-30% (4). Mortality approaches 50% if necrosis of the gland is greater than 50% and can further increase up to 80% if sepsis occurs (5). Approximately half of the deaths in acute pancreatitis occur within the first two weeks of illness and are mainly attributed 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. An important meta-analysis on mortality was published by Petrov et al (6). In patients with acute pancreatitis the absolute influence of organ failure and infected pancreatic necrosis on mortality were the same. Both indicate severe disease. If both are present the relative risk of mortality doubles.
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, the severity of pancreatitis and the 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 (7-11). 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**) (9), or a score of 8 or more in the APACHE II-Score, and evidence of organ failure and intrapancreatic pathological findings (necrosis or interstitial pancreatitis) (**Table 2**). This classification is helpful because it also allows the comparison of different trials and methodologies (11). 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 3**) (10). 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 30% 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 (12). Another predictive factor on mortality was recently published. The blood urea nitrogen levels (BUN) in the first 48 hours of hospitalisation were persistently higher among non-survivors than survivors. It seems that BUN is a new and valuable marker for predicting mortality (13).
In the last few years, more complicated scoring systems have been proposed for predicting persistent organ failure. They are more accurate but are too complicated for routine clinical use (14).

Table 1
Ranson's criteria of severity for acute pancreatitis (9)

Admission criteria Age > 55 years WBC > $16.0x10^9$/L Glucose > 10 mmol/l (180 mg/dl) Lactate dehydrogenase (LDH) > 350 IU/L Aspartamine Transaminase (AST) >250 U/L
Following initial 48 hours Criteria Haematocrit decrease of >10% BUN increase of > 1.8 mmol/l (5.1 mg/dl) Calcium < 2 mmol/l (4 meq/l) PaO_2 < 60 mmHg (8 kPa) Base deficit > 4 mEq/L Fluid sequestration >6 L

Table 2
Atlanta classification (11)

Atlanta Classification **(Defining Severe Acute Pancreatitis)** **- Evidence of Organ Failure** Shock (Systolic Blood Pressure <90 mm Hg) Pulmonary insufficiency (PaO2<60 mm Hg; 8kPa) Renal failure (creatinine > 2mg/dl; 177umol/l) Gastrointestinal bleed (>500 ml/day) **- Or Local Complications** Pancreatic necrosis >30% Pancreatic abscess Pancreatic pseudocyst - **With Unfavorable Prognostic Signs** Ranson Criteria $\geq$3 or APACHE II score $\geq$8

Table 3
Computed tomography (CT) grading system of Balthazar (10)

CT grade		**Quantity of necrotic pancreas**
Grade A = **0**	Normal appearing 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

Undernutrition and obesity are often seen 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 male acute pancreatitis patients (30-40%) (15). Patients with biliary pancreatitis, more dominant in women, have a high tendency to be overweight.

For nutritional support, it is therefore necessary to assess the severity of acute pancreatitis and the nutritional status at the time of admission and during the course of the disease. Both factors are necessary to plan nutrition interventions in patients with acute pancreatitis.

3. Energy and Substrate Metabolism during Acute Pancreatitis

Specific and non-specific metabolic changes occur during acute pancreatitis. A variety of proinflammatory cytokines increases the basal metabolic rate. This can result in increased energy consumption. The resting energy expenditure varies according to the severity and the duration 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 determines negative clinical outcome (16). Whether negative nitrogen balance is the principle factor for outcome is not clear. The relationship between nitrogen balance and outcome may only reflect the relationship between nitrogen balance and severity of disease. There is no 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 the SIRS response, oxidative stress, and insulin resistance. The resultant futile fluid cycling and milieu of inflammatory cytokines may cause an increase in energy demand. Endogenous gluconeogenesis is increased as a consequence of the metabolic response to the severe inflammatory process.

Glucose is an important source of energy and can partially counteract the intrinsic gluconeogenesis from protein degradation. This can counteract, to a certain degree, the deleterious and unwanted effect of protein catabolism (17). The maximum rate of glucose oxidation is approximately 4 mg/kg/min. The administration of glucose in excess can be wasteful, and even harmful, because of lipogenesis and glucose recycling. Furthermore, hyperglycaemia and hyperkapnia can occur. Hyperglycaemia is a major risk factor for infections and metabolic complications. Monitoring and control of blood glucose is therefore essential. Evidence of glucose intolerance occurs in the majority of cases (incidence 85%) (18).

3.2 Protein Metabolism

A negative nitrogen balance is often seen in severe acute pancreatitis. The protein losses must be minimized and the increased protein turnover must be compensated. If acute pancreatitis is complicated by sepsis, up to 80% of the patients are in a hypermetabolic state with an increase of the resting energy expenditure. A negative nitrogen balance is associated with adverse clinical outcome. Nitrogen losses are as much as 20-40 g/day in some patients with acute pancreatitis.

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 concentrations return to normal ranges. Evidence of fat intolerance occurs only in 12-15% of cases (18). It is also known that in some patients with severe hyperlipidaemia an acute pancreatitis can develop (19).

4. Exocrine Pancreatic Stimulation by Macronutrients

In general all forms of enteral nutrition can stimulate the exocrine pancreatic secretion to some extent. Only with parenteral nutrition is this not the case (20, 21). For nutritional intervention the administration of glucose, protein and fat are necessary, but for a long time enteral applications were considered to be harmful because of the potential stimulation of the exocrine pancreatic enzyme secretion.
Enteral glucose perfusion into the jejunum is however a very weak stimulus for exocrine pancreatic secretory response. Jejunal perfusion of elemental diets containing defined amounts of amino acids are well tolerated and do not stimulate exocrine pancreatic secretion (22, 23). The stimulation of the exocrine pancreatic secretion by enteral administration of lipids depends on the level of infusion within the GI tract. If the lipids are given into the proximal jejunum, only a minimal stimulation of the exocrine pancreatic secretion occurs. The implications for therapy are that with any feeding within the GI tract, changing the content (decreasing the protein complexity or reducing the chain-length of fat) or changing the level of infusion (lower in GI tract below the Ligament of Treitz) results in a shift of the balance by invoking fewer stimulatory factors and a greater number of inhibitory factors.

The intravenous infusion of macronutrients concerning exocrine pancreatic stimulation is safe (24, 25). The administration of glucose intravenously does not stimulate exocrine pancreatic secretion. The main risk of intravenous glucose in acute pancreatitis is hyperglycaemia. Hyperglycaemia can also be aggravated due to the insulin resistance in critical ill patients. Intravenous applications of protein hydrolysates have shown an inhibition of exocrine secretory responses or no effect. Pancreatic exocrine secretion is not stimulated by intravenous lipids. The only concern of potentially exacerbating acute pancreatitis with intravenous PN is through the development of hypercalcaemia or hypertriglyceridaemia. Compared to delivery of the same nutrients intravenously, an enteral infusion results in a greater insulin response, less insulin resistance, and less hypertriglycaeridemia due to the enteroinsular pathway.

All these findings have changed the nutritional concept in acute pancreatitis. Nowadays, enteral feeding into the jejunum 20-120 cm beyond the ligamentum of Treitz is regarded to be safe without major stimulation of autodigestive processes in the pancreas and maintaining the gut integrity by modulating the GI-tract systemic immunity.
In addition it was shown in animal studies, that the exocrine secretion in acute pancreatitis is reduced (26). It seems that in severe acute pancreatitis the secretory response to enteral nutrition is suppressed enough to allow the inflammation to resolve, even with continued delivery of EN. This finding implies that we do not have to get to unstimulated basal levels of pancreatic exocrine secretion for the inflammatory process to abate (26, 27).

5. Energy Requirements

Patients with severe acute pancreatitis are hypermetabolic. The more severe acute pancreatitis is, the more excessive is the hypermetabolism. Resting energy expenditure can be variable in these patients. A range from 77-158% of the predicted energy expenditure has been reported (28). If the disease is complicated by sepsis or multiorgan failure, the resting energy expenditure is significantly increased.
It was shown that in severe acute pancreatitis, the Harris-Benedict equation is not sensitive enough to estimate the caloric expenditure. In these cases, indirect calorimetry is recommended to avoid over- or underfeeding.
For enteral or parenteral nutrition, 25-35kcal/kgBW/d is recommended. Overfeeding and hyperglycaemia should be avoided. Blood glucose concentration should not exceed 10 mmol/l (180 mg/l). Insulin treatment is recommended, but the doses should not be higher than 4 to 6 units/h. The impaired glucose oxidation rate cannot be normalized by insulin administration. Normally, 3-6g/kgBW/d of carbohydrates can be recommended.
The optimal goal of protein supply is 1.2 to 1.5g/kgBW/d. A lower protein intake should only be given to patients with renal or severe hepatic failure.
Fat can be given up to 1g/kgBW/d, but blood triglyceride levels must be monitored carefully. Triglycerides are tolerated up to 12 mmol/l (1090 mg/l). However, the ideal concentration of plasma triglycerides should be <4 $mmol \cdot l^{-1}$(363 mg/l) due to metabolic problems unconnected with pancreatic problems but connected with hypertriglyceridaemia (**Table 4**).

Table 4

Substrate	**Quantity**
Energy	25–35 $kcal \cdot kg^{-1} \cdot d^{-1*}$
Protein	1.2–1.5 $g \cdot kg^{-1} \cdot d^{-1}$
Carbohydrates	3–6 $g \cdot kg^{-1} \cdot d^{-1}$ corresponding to blood glucose concentration (aim for <10 mmol/l)*
Lipids	Up to 1 $g \cdot kg^{-1} \cdot d^{-1}$ corresponding to blood triglyceride concentration (aim for <4 $mmol \cdot l^{-1}$)*

*Overfeeding should be avoided, especially in obese patients, possibly according to measured resting energy expenditure (REE; indirect calorimetry)

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 (29-36). In mild to moderate acute pancreatitis these studies showed no effect on outcome (29, 30). 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. In the last few years, 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 hyperglycaemia with insulin reduced mortality in critical care patients (37).

Recently, the nutritional management shifted from parenteral to enteral feeding. Enteral feeding in acute pancreatitis may reduce catabolism and loss of lean body mass and may modulate the acute phase response with the potential to down-regulate splanchnic cytokine response (38) (**Table 5**).

Table 5
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 the 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 severe acute pancreatitis, the results were different from those in mild to moderate pancreatitis. In the first prospective study, by Kalferanzos et al, comparing naso-jejunal tube feeding with a semi-elemental diet with TPN started 48 hours after admission, 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 (31). These findings are supported by several other studies (31-34). The study of Windsor et al (32) 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 afterward. 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. The randomized patients in the enteral group were fed for a significantly shorter period (6.7 days vs. 10.8 days), had significantly fewer metabolic and septic complications. In addition, hyperglycaemia requiring insulin therapy was significantly more common in the parenterally fed patients (33). 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 (35). There is only one study, by Doley et al, showing comparable results with enteral and parenteral nutrition in 50 patients with severe acute pancreatitis in terms of hospital stay, infections, need for surgery and mortality (36).
Today, there is no doubt, that enteral nutrition should be the first attempt to feed patients with severe acute pancreatitis. There is a clear improved risk/benefit ratio with enteral nutrition compared to TPN. The first meta-analysis from McClave et al (39) showed that the use of enteral nutrition was associated with a significant reduction in infectious morbidity, a reduction of hospital length of stay and a trend toward reduced organ failure when compared with the use of parenteral nutrition. There was no effect on mortality. In three systematic reviews and meta-analysis Petrov et al came to the same conclusions and found even a reduction of mortality for enteral nutrition in the severe cases (40-42). The early start of enteral nutrition yielded significant reduction in multi-organ failure, pancreatic infectious complications and mortality compared to a later start (41). Overall, in 9 studies the mortality and in 7 studies the infectious complications were reduced (43). In cases where enteral nutrition is not possible TPN has to be used. The guidelines from the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) suggest waiting 7 days (43). The ESPEN experts recommend starting earlier: after 3-4 days (44). The study from Xian-Li supports this approach. TPN

was started 24-48 hours and they found reductions of overall complications, hospital stay and mortality (45).
Intolerance to enteral feeding can be prevented by starting enteral nutrition as early as possible. Avoid bolus feeding and use continuous feeding over 24 hours.
If there is intolerance and you started with gastric feeding, change to jejunal feeding and if you started with a polymeric formula, change to peptide-based formula with MCTs and very low fat content.

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 (44, 46). Enteral nutrition is unnecessary if the patients will be able to consume normal food after 5 to 7 days (ESPEN Guidelines: Grade B). Indeed up to 80% are on an adequate oral diet within 7 days (29). For refeeding, a normal diet with a reduced fat content is recommended. A transition with a liquid diet is not necessary (43).
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 early refeeding in 5 to 7 days is not possible. **Fig. 1** shows a frequently used approach for these patients.

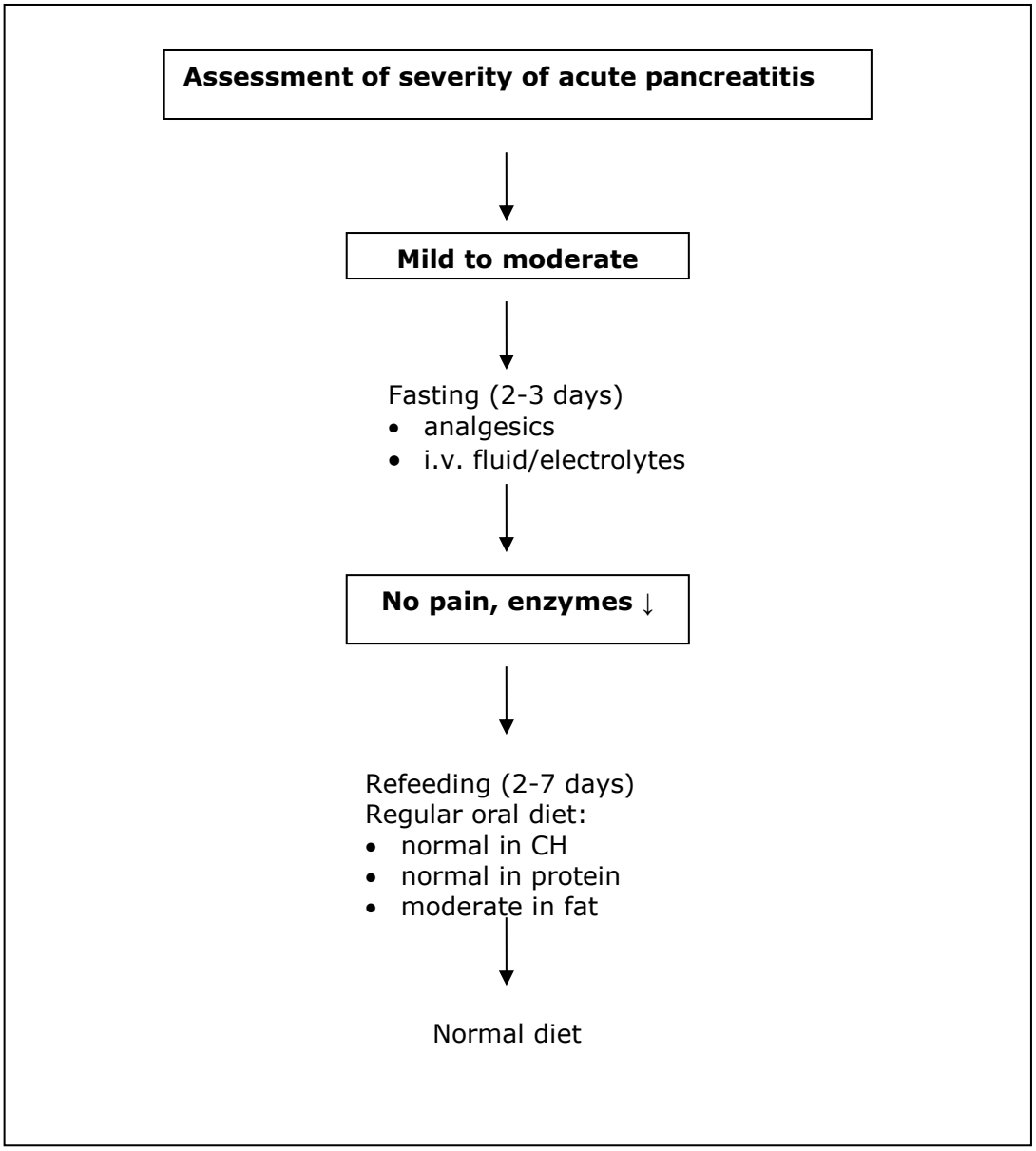

Fig. 1 Management for mild acute pancreatitis

8. Nutritional Support in Severe Acute Pancreatitis

In patients with severe pancreatitis, who have complications or need for surgery, early nutritional support is needed to take advantage of the window of opportunity by which EN can favourably alter patient outcome. In severe necrotizing pancreatitis, enteral nutrition is indicated first if possible (ESPEN Guidelines: Grade A, (44, 46). In the last decade, the nutritional strategy in acute pancreatitis has changed. The nutritional management has shifted from parenteral to enteral nutrition. Enteral feeding in acute pancreatitis has been shown to reduce catabolism and loss of lean body mass, and to modulate the acute phase response, with the potential to down regulate the splanchnic cytokine response (31). Furthermore, enteral nutrition has been shown in many studies to be safe and well tolerated. Several prospective, randomized clinical trials have been performed comparing enteral with parenteral nutrition in patients with severe acute pancreatitis (38). In patients with severe necrotizing pancreatitis, the full amount of nutrient delivery by the enteral route is not always possible. If complete enteral nutrition is not possible, this nutritional support should be combined with parenteral nutrition (44, 46). Usually, the combined nutritional support allows the patient to reach the nutritional goals. The administration of

fat in parenteral nutrition can be regarded as safe if hypertriglyceridaemia (<12 µmol/l; 1090 mg/dl) is avoided (44, 46).
In the few last years, the nature of enteral nutrition in severe acute pancreatitis has been newly defined. Jejunal feeding is not always necessary, and gastric or even oral feeding is sometimes possible (see Chapter 8.1)
A practical approach for nutrition in severe acute pancreatitis is outlined in **Fig. 2**.

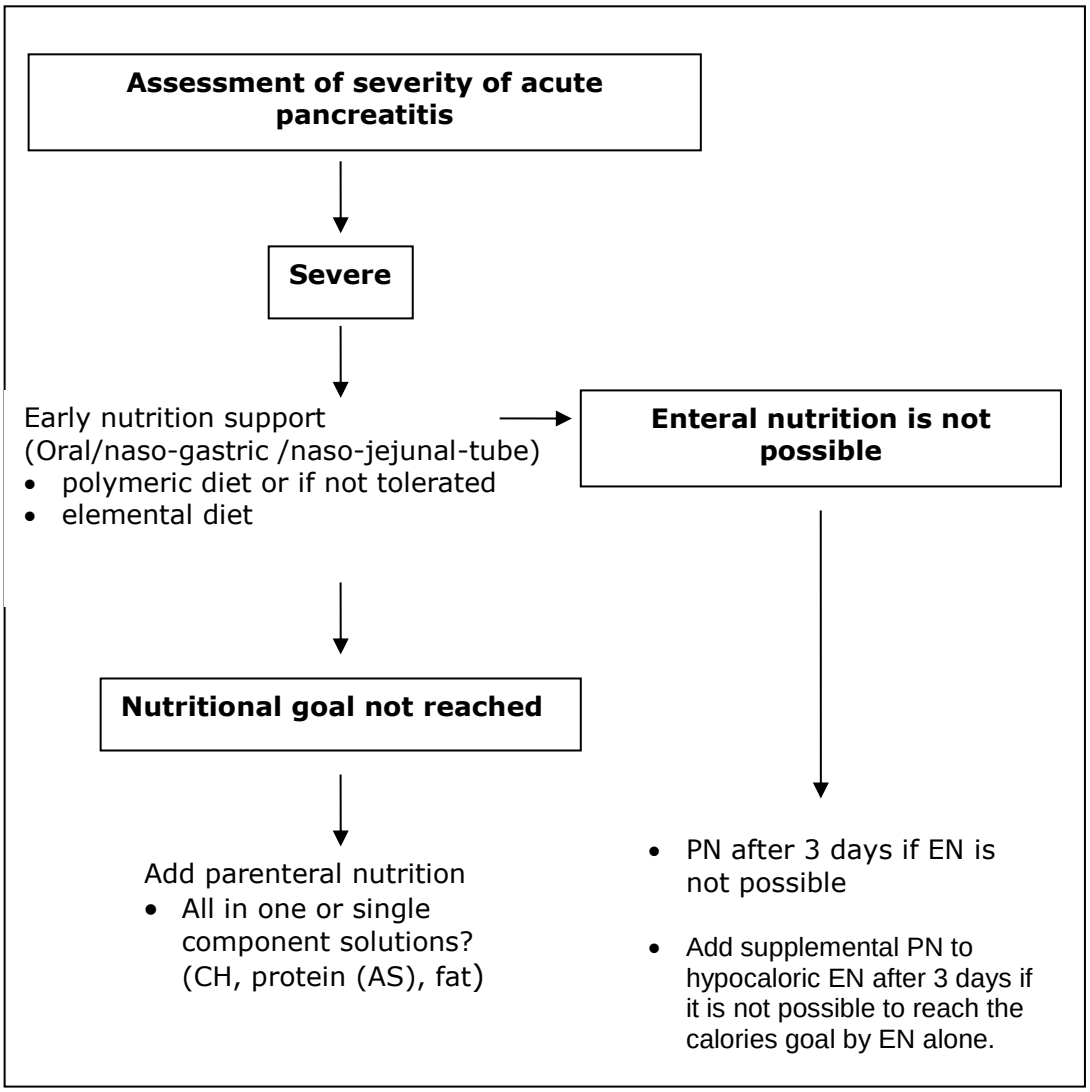

Fig. 2 Management for severe acute pancreatitis

8.1 Route of Feeding

The route of nutrient delivery (parenteral/enteral) should be determined by the severity of the attack and the patient's tolerance. Tube feeding is possible in the majority of patients, but some patients need the combination with parenteral nutrition (ESPEN Guideline: Grade A). Several prospective studies have shown that in severe acute pancreatitis jejunal tube feeding is possible in most patients (44). Placing a jejunal feeding tube distally to the ligament of Treitz can easily be performed. The tubes are placed either with fluoroscopic help or more easily with the endoscope. Another way is to use self-propelling nasojejunal feeding tubes. Normally, jejunal tubes are well tolerated (30, 47-49). Hegazi et al reported that early initiation of distal jejunal feeding was associated with reduced mortality in patients with severe acute pancreatitis. The early achievement of the feeding goals was also associated with a shorter length in the ICU (50). Rarely, proximal migration of the

feeding tube and subsequent pancreatic stimulation can aggravate acute pancreatitis (51). Partial ileus is not a contraindication for enteral feeding because these patients frequently tolerate continuous low-volume jejunal nutrients. Several single or multilumen tubes are available (**Fig. 3**). Multilumen tubes with one port in the stomach and one port in the jejunum have the advantage that the administration of enteral formulas can be amended according to the tolerance. In the case of surgery for pancreatitis an intra-operative jejunostomy (**Fig. 4**) for postoperative tube feeding is feasible (52).

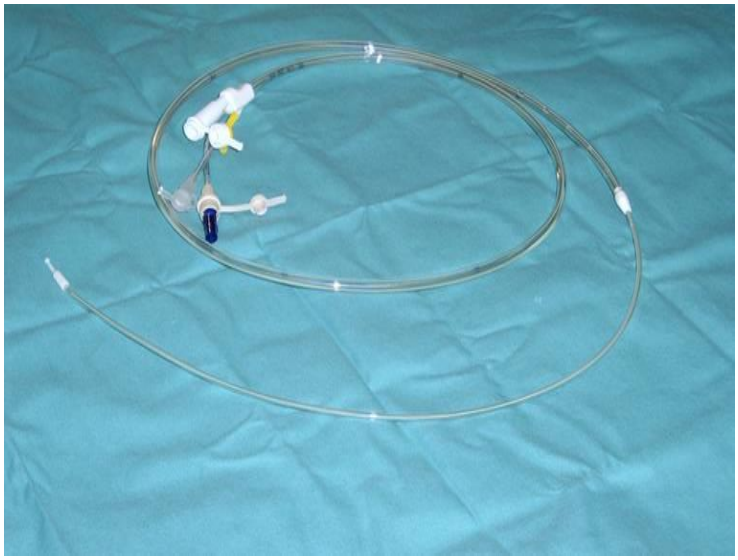

Fig. 3 Multilumen nasojejunal tube

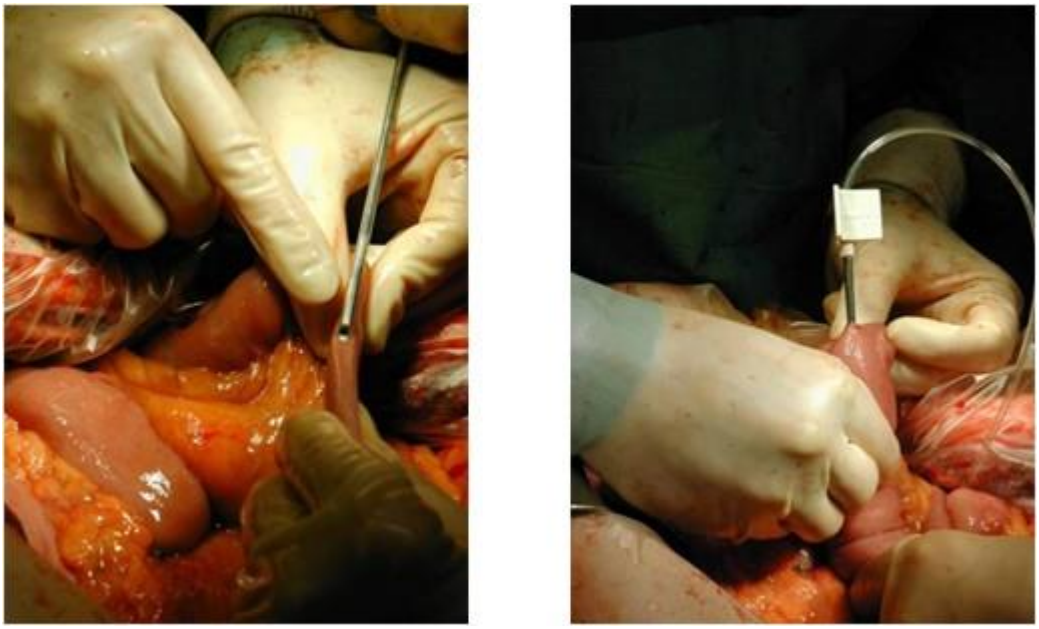

Fig. 4 Fine needle catheter-jejunostomy

8.1.1 Jejunal, Gastral or Oral Feeding

Jejunal feeding is not always necessary. Minimizing stimulation of exocrine pancreatic secretion would support the jejunal feeding route. It is, however, controversial whether stimulation of pancreatic secretion is important for the outcome in this disease. Eckerwall et al studied the role of immediate oral feeding versus fasting in 60 patients with acute pancreatitis (53). After fluid resuscitation the patients were fed orally. In this group the period of intravenous fluids, the time to introduction of solid food, and the length of hospital stay were significantly shorter than in the fasting group. There was no difference in

symptoms or complications. Bakker et al compared early versus on-demand nasoenteric tube feeding in patients with acute pancreatitis. In this multicentre study with 208 patients early nasoenteric tube feeding was compared with an oral diet after 72 hours. They found no superiority of an early nasoenteric tube feeding compared to the oral diet. The complications and mortality were not different (54).
Four randomized studies comparing naso-gastric versus naso-jeunal feeding or naso-gastric versus TPN in severe acute pancreatitis have been published (55-58). 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, nutritional intolerances, serum CRP concentration, or mortality (55-57). Compared to parenteral nutrition there were significantly more complications in the first 3 days in the naso-gastric group, but there was a better control of blood glucose levels (58). Petrov et al published a systematic review including all studies (59). Gastric feeding was safe, and in the majority (79%) it was well tolerated without a statistically difference in clinical outcome.
The meta-analysis by Chang et al found no clear differences between gastric and jejunal feeding in terms of outcome (60).
Clear recommendations cannot be given. A useful approach in patients who have or will develop a severe form of pancreatitis could be:

1. **Try to start early (48-72 hours) with an oral nutrition regimen**
   If not tolerated
2. **Place a multilumen tube and start with gastric feeding**
   If not tolerated
3. **Start jejunal feeding**

More clinical trials using such concepts are warranted.
The advantage of gastric feeding is to facilitate delivery of EN, reduce time to initiation of feeding, and minimize chances for ileus and intolerance. The limitations of jejunal feeding are the need for expertise in tube placement below the ligament of Treitz. There is little harm and no real downside from this strategy of gastric feeding, as evidence of intolerance can be ameliorated by adjustments in level of infusion and content of formula.

8.2 Which Enteral and Parenteral Formula

Most studies in the past have been done using peptide-based or elemental formulae. The use of these formulae showed beneficial effects (ESPEN Guidelines: Grade A) (44). Nowadays in most institutions polymeric formula are used although only few data are available here. Windsor et al and Pubelis et al have shown that polymeric formulas can safely be given through a jejunal tube in patients with acute pancreatitis (32, 61). Only few direct comparisons of a peptide-based formula with a polymeric formula are published (47, 61). Cravo et al found a similar tolerance in 102 patients with acute pancreatitis for both formulas (47). Tiengou et al showed that there was no difference in tolerance, but in the semi-elemental group the weight loss was less, and the length of hospital stay was shorter (62). Today, it is common to start with a standard polymeric formula, and if this is not tolerated, a peptide-based formula is tried. The meta-analysis from Petrov et al supports this approach. They concluded that a polymeric formula compared to a (semi)elemental formula showed no significant higher risk of feeding intolerance, infectious complication or mortality in acute pancreatitis patients (63). In addition the polymeric formulas are less expensive. The use of polymeric formulas was also recommended by the new guidelines from the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) (43).

Several published trials used also formulas containing immune modulating substrates (glutamine, arginine, n-3 polyunsaturated fatty acids, vitamins and minerals) or pre- and probiotics.

Hallay et al studied the effect of enteral glutamine supplementation (64). They found a faster recovery of immunological parameters and a shorter recovery period from the disease in the glutamine group. In another study glutamine, arginine, n-3 fatty acids and antioxidants were given (65). In this study, the outcome was not statistically different. The supplementation of n-3 fatty acids alone in moderately severe acute pancreatitis significantly lowered the length of hospital stay, and the need for nutritional therapy. The overall complication rate was not different (66). At present, these formulas cannot be generally recommended because these data need confirmation with studies including larger numbers of patients.

The concept of using pre- and probiotics to prevent intestinal bacterial translocation is very attractive. Two studies by Olah et al examined the efficacy of enteral administration of probiotics in patients with severe acute pancreatitis (67, 68). In the first study, 22 patients received live Lactobacillus plantarum and oat fibre, and 23 patients the same formulation with heat-killed bacteria. In the group with live bacteria they found fewer positive cultures ($p = 0.23$), less need for antibiotics, fewer pancreatic infections and less requirement for surgical interventions ($p = 0.046$). Furthermore, the length of hospital stay was shorter (13.7 d vs. 21.4 d) (67). In the second study, they randomized 62 patients with acute pancreatitis who were fed with a naso-jejunal tube. 29 patients received only enteral nutrition with fibre. 34 patients were treated with enteral nutrition with fibre and a combination of four different lactobacilli. The treatment group again had significant lower complication rates ($p = 0.049$). The control group had higher multiorgan failure, pancreatic septic complications, surgical intervention rate and mortality (68). These observations were exciting until the large multicenter controlled trial by Besselink et al was published (69). They randomized 298 patients with severe acute pancreatitis with either a combination of 6 probiotics (4 strains lactobacilli and 2 strains bifidobacteria) or placebo. A multi fibre enteral solution was given in both groups by a naso-jejunal tube. There were no differences in infectious complications between the probiotic and placebo group (30% vs 28%). Unfortunately, mortality was significantly higher in the probiotic group (16 vs 6%). Nine patients in the probiotic group developed bowel ischaemia. At the moment it is not clear if these complications are due to the combination of probiotics administered to the gut or if other underlying factors have played a role (70). The two groups were not fully comparable. Organ failure during admission was more common in the probiotic group than in the placebo group (27.0% vs 16.0%; $p=0.02$). Intestinal ischaemia can also be found more often during vasopressor treatment. In the probiotic group more patients received vasopressor drugs than in the placebo group. This could be another explanation for the developing of bowel ischaemia. In the Besselink study no adverse events were shown in the group receiving only prebiotics. This is in line with a new study published by Karakan et al (71). They found that naso-jejunal enteral nutrition with prebiotic fibre supplementation in patients with severe acute pancreatitis improved hospital stay, duration of nutrition therapy, acute phase response and overall complications compared to standard enteral nutrition.
How can we explain the different outcomes in the Olah and the Besselink study? There are some speculations. In the Besselink study, they applied very high concentrations of probiotic over four weeks. In addition, they included for the first time bifidobacteria. Maybe the high amount of probiotics together with the high amount of fibre increased the fermentation in the small bowel too much. Some of the patients were haemodynamically compromised and on vasoactive treatment. An increased gas production could lead to more distension and maybe to intestinal ischaemia. In addition, in the Olah studies, the patients' underlying pathology was mainly alcohol-induced pancreatitis, whereas in the Besselink study, more patients had gallstone induced pancreatitis. It is known that the course of the disease in acute alcoholic pancreatitis is different from gallstone pancreatitis. A new meta-analysis from Zhang et al in 2010 including seven randomized studies with 559 patients showed no influence on reduction in postoperative infectious complications, pancreatic infection, MOF/SIRS, and mortality with probiotics/synbiotics compared with placebo. However, pre-, pro- or synbiotics treatment was associated with a reduced length of hospital stay (72). In addition, a large study with 183 patients by Wang et al in 2013

showed a significant reduction in pancreatic sepsis and MOF. Mortality was not different (73). The guidelines from the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) concluded that the use of probiotics could be considered in patients with severe acute pancreatitis who are receiving early enteral nutrition (43). The remaining problems we still have is the lack of a standardized commercial product. Different probiotics with different dosages have been used in all the studies.

Several studies were done in the past by supplementation of TPN with n-3 fatty acids or glutamine. Wang et al found that patients treated with TPN containing n-3 fatty acids had significantly higher EPA concentrations, lower CRP levels, and better oxygenation index after 5 days than the control group. In addition the number of days of continuous renal replacement therapy was significantly decreased (74).
Xiong et al found in the group treated with TPN and n-3 fatty acids, that the fluid equilibrium time became shorter, and that the SIRS scores were decreased, and vanished after the fourth day. In addition the unbalanced pro-/anti-inflammatory cytokine levels improved (75).
Five earlier studies using glutamine supplemented TPN demonstrated beneficial effects.
Ockenga et al found a reduction of the C-reactive protein level, a reduced length of TPN and a favourable trend in the length of hospital stay (76). Xian-li et al could show a reduction of mortality, and the incidence of infectious complications. Furthermore, the length of hospital stay was shorter, and the nutritional status improved compared with the non-supplemented group (77). Sahin et al demonstrated a significant reduction in complications (10 vs 40%) without changing the length of TPN or the hospital stay (78). This was confirmed by the study from Fuentes-Orozco et al (79). The group with glutamine supplementation had a significant increase in serum IL-10 levels, total lymphocyte and lymphocyte subpopulations counts, and albumin serum levels. Nitrogen balance improved to positive levels in the study group and remained negative in the control group. Infectious morbidity was more frequent in the control group. The duration of hospital stay and the mortality were similar between the two groups. Xue et al evaluated the effect of glutamine given early or late in patients with severe acute pancreatitis. They found a significant benefit for the early supplementation of glutamine. They showed a reduction of the presence and duration of organ failure, the incidence of infection, the need for surgery, and mortality (80). A new meta-analysis including 10 studies by L Yong et al showed significant effects in raising the albumin levels, and decreasing the CRP levels, infectious complications, LOHS and mortality (81).

It can make sense in the future to add n-3 polyunsaturated fatty acids and/or glutamine if patients with severe acute pancreatitis need TPN.

9. Oral Refeeding

There are only few 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 with several meals given during the day.
Only few studies have investigated oral refeeding. In the first 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. Pain relapse resulted in doubling the length of stay in the hospital (82). Pandey et al compared oral with jejunal refeeding in a randomized study (83). No pain relapse was found in the jejunal group, whereas 4 out of 15 patients in the oral group developed pain again. Jejunal feeding was started after a median of 7 days, and oral feeding a median of 5 days after the onset of pain. Pain relapse was associated with longer duration of initial pain and a higher CT severity index. Chebli et al reported similar results. They found that predictors of refeeding

pain included peripancreatic fluid collections, serum CRP on the fourth day, and serum lipase level on the day of starting oral refeeding (84). In a large study, 274 patients were evaluated by Petrov et al (85). An oral diet was started when abdominal pain was controlled and there were no signs of an ileus. In 60 patients (21.9%) pain recurred. In 76% this was seen within 48 hours of starting oral refeeding.
In three randomized prospective studies, the composition of the diet for refeeding was investigated in patients with mild pancreatitis (86-88). Jacobson et al. compared a clear liquid diet (588 kcal/2 g fat) with a low fat solid diet (1200 kcal/35 g fat) in 121 patients (86). Sathiaraj et al. compared a clear liquid diet (458 kcal/11 g fat) with a soft diet (1040 kcal/20 g fat) in 101 patients (87). In both studies, there was no difference in tolerance and clinical outcome but the patients with the low fat solid diet and the patients with the soft diet consumed significantly more calories and fat during the first meal compared to the liquid diet groups. The results were different for the length of hospital stay. In the Jacobson et al. study there was no difference for the two diets, but in the Sathiaraj et al. study the length of hospital stay was significantly shorter with the soft diet (86, 87). These results were recently confirmed by a prospective randomized controlled double blind study using different kinds of diets from liquid to normal (88).
Teich et al. published an interesting study in patients with mild acute pancreatitis (89). In an open randomized multicentre study 143 patients were either re-fed according to the current guidelines (no pain, normal serum lipase levels) or feeding was started according to the wish of the patients. In the group where the patients could decide to start refeeding the intake of the first meal was one day earlier (2 days [IQR 1-3 days vs. 3 days] IQR 2-4 days; $p < 0.05$). There were no differences in pain relapse and the length of hospital stay between the two groups. Both regimens were very well tolerated.

Overall, the data on refeeding are interesting but still not sufficient to give clear recommendations on the optimal time of starting oral nutrition and the type of the diet. Clinicians should consider advancement to oral diet when pain is resolving or gone and enzymes nearly normalized. Although clear liquids theoretically should be tolerated better, the incidence of tolerance surprisingly is no different from that with soft diet. The rate of advancement of the diet may be directed by patient wishes. An exacerbation of symptoms after advancement may simply reflect that inflammation has not yet completely resolved within the pancreas.

10. Nutritional Support in Patients after Pancreatic Surgery

Postoperative feeding with a needle catheter jejunostomy was successful in several small studies (48, 52, 90). Hernandez-Aranda et al found no difference between groups of patients who received postoperative parenteral nutrition or enteral nutrition via jejunostomy (90). Furthermore, in patients undergoing surgery for severe acute pancreatitis, needle catheter jejunostomy for longterm enteral nutrition was safely applied with no nutritional risk (52). In general, in these patients, nutritional support has to be planned before the operation according to the clinical situation and the course of the disease (39).

11. Summary

75-80% of patients with acute pancreatitis have 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 and GI-disturbances. The best time and the best composition of the diet are still not clear. There is no evidence that a specific enteral or parenteral nutrition is of benefit in patients with mild to moderate pancreatitis. There are no data available to give a nutritional recommendation in patients with severe pre-existing malnutrition or who are overweight.
Patients with severe disease, complications, or the need for surgery require early nutritional support. In patients with severe pancreatitis, an enteral (oral, gastral or jejunal)

approach should be established, but parenteral nutrition is an alternative method, when enteral nutrition is insufficient. For the future, more aggressive use of pharmaconutrition may be employed to modulate epigenetics and activate the body's own antioxidant response elements to reduce oxidative stress. Several factors have to be clarified: The optimal timing of nutritional therapy, the optimal feeding site (oral, gastric, jejunal or TPN), the optimal nutrient formulation (semi-elemental diet, polymeric diet, immune-enhancing diet, pre- and probiotics). Furthermore, in new studies a clear stratification of the patients according to their nutritional status on admission should be performed.

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