

CONSENSUS STATEMENT

ESPEN guidelines on nutrition in acute pancreatitis

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Introduction

The two major forms of inflammatory pancreatic diseases – acute and chronic pancreatitis – are different entities which require different nutritional approaches. Despite increasing knowledge in the fields of metabolism, clinical nutrition, and intervention, there is still a lot of controversy with respect to the optimal approach concerning treatment regimens. It is generally accepted that nutritional management depends on the underlying pancreatic disease. For many years, textbooks have suggested that oral or enteral feeding may be harmful in acute pancreatitis; feeding was thought to stimulate the exocrine pancreatic secretion and consequently autodigestive processes. On the other hand, it is known that nutritional deficiencies can occur in patients with a prolonged and complicated course of an acute necrotizing pancreatitis. Furthermore ~30% of patients with acute pancreatitis are already malnourished at the time of the initial attack (1). It has also been questioned whether early feeding changes the outcome in uncomplicated acute pancreatitis. Thus far, there is no generally accepted or standardized approach for handling nutrition in patients with acute pancreatitis.

With this background, ESPEN invited a group of gastroenterologists, pancreatologists, intensive care specialists, and nutritionists to prepare guidelines and a consensus report on nutritional strategies in patients with acute pancreatitis. The aim of this consensus was to share current knowledge from physiology and patho-

physiology, to develop common terminology, to obtain consensus criteria to be adopted in clinical trials, and finally to stimulate cooperative European research.

Physiology and pathophysiology of pancreatic secretion and consequences for nutrient digestion

Digestion of food and absorption of nutrients are a complex and finely coordinated process which require multiple and integrated gastrointestinal secretory absorptive motor and circulatory systems (2, 3). The pancreas plays a central and crucial role: its intact function is one of the prerequisites for adequate processing and mucosal uptake of nutrient components.

Physiology of pancreatic secretion and luminal nutrient digestion

The normal human pancreas secretes more than 10 different enzymes together with water, bicarbonate, and other proteins (such as secretory enzyme inhibitors). These enzymes are secreted in abundance and hydrolyze within the intestinal lumen macronutrients of which lipids, protein, and carbohydrates are of particular importance. For an undisturbed digestion, not only the quantity of the secretory response is necessary, but even the timed, controlled, and coordinated release of these enzymes into the duodenal lumen in response to a meal is required. Postprandially, regulation of human pancreatic secretion must be seen as part of an overall integrated motor and secretory response (4). Whilst a meal is the most important physiologic stimulus, pancreatic secretion also occurs in the fasting (inter-digestive) state in a precisely regulated and coordinated fashion (5).

Pancreatic response and luminal nutrient digestion following meal ingestion

Human pancreatic enzyme output reaches maximal rates following a mixed meal of 20 kcal/kg body weight,

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but the duration of the response increases with greater caloric loads (6). The pancreatic response is also influenced by the physical properties of the meal: mixed solid-liquid meals induce a longer response than homogenized or liquid meals with a similar energy content (7-9). In both instances, the rate of gastric retention and thus duodenal delivery of stimulatory nutrients are the key factors which determine the duration of pancreatic secretion underscoring the regulatory importance of the interaction of gastrointestinal motor and pancreatic function. Proportions of fat, carbohydrate, and protein contents within a meal also influence the duration and enzyme composition of the pancreatic response in humans (10). The overall quantity of enzyme secreted exceeds by far the minimal amount required to avoid manifest nutrient malabsorption (4, 11).

Digestion of nutrients commences prior to the exposure of chyme to pancreatico-biliary secretions, although it is not precisely clear and is partly controversial to what extent salivary amylase, pepsin, and gastric lipase contribute to the degradation of carbohydrate, protein, and fat (2, 3, 12-14). It is conceivable and supported by experimental evidence that pepsin and gastric lipase are more important for digestion during pathological conditions such as acute or chronic pancreatitis. Yet, in humans, the finely tuned gastric emptying of portions of preprocessed, liquid chyme into the duodenum starts the pivotal period of intraluminal digestion. Under physiologic conditions, the duodenal entry of nutrients is accompanied by bursts of pancreatico-biliary digestive secretions with which nutrients are instantly mixed and exposed to a large mucosal area, and digestion; subsequent absorption occurs rapidly. As a result, up to 70-80% of the cumulative prandial nutrient load may have been absorbed from the lumen as proximal as at the duodeno-jejunal junction (7, 12, 15-17).

It is important to note that the generation of products that occurs as a result of the intraduodenal digestive process is the key event for the regulation and integration of the postprandial gastrointestinal response. It activates multiple postprandial neuro-humoral mechanisms controlling motor (e.g. feedback control of gastric emptying rate) and secretory (e.g. pancreatic and bile output) as well as metabolic (e.g. release of insulin and other hormones) responses. Indeed, decreased intraduodenal nutrient digestion is associated with disturbed postprandial regulation of hormone release and motility responses (16). Paradoxically, even under physiologic conditions, a proportion of ingested nutrients remains unabsorbed within the small intestine (7, 18). This 'physiologic malabsorption' is assumed to contribute to the energy supply of the distal small intestinal and colonic mucosa. Therefore, the distal bowel participates in the integrated gastrointestinal secretory, motor, and metabolic postprandial responses.

Regulation of postprandial pancreatic response

While a vagally mediated cephalic phase contributes up to 40% of the overall pancreatic response, the most important mechanism is the presence of nutrients within the duodenal lumen (intestinal phase). Maximal enzyme outputs are observed both with and without experimental diversion of postprandial chyme at the ligament of Treitz (19). On the other hand, intrajejunal nutrients also elicit a marked stimulation of human pancreatic secretion. This normally redundant mechanism may become important in patients with gastrojejunostomies, those with resected or bypassed antroduodenal segments (e.g. Billroth II, Roux-en-Y) and those with jejunostomies (4).

Mediation of postprandial stimulation of human pancreatic secretion by duodenal nutrients involves the activation of neural pathways, in particular, vagal-cholinergic reflexes, and release of regulatory peptides, in particular, cholecystokinin (CCK), with a tight interaction of neural and humoral systems. The current concept assumes that CCK may act both as a stimulatory neuromodulator of the cholinergic pathway, and as a hormone (4, 20-22). The regulation of human postprandial pancreatic exocrine secretion also involves inhibitory mechanisms that eventually terminate the response. These are induced by nutrient exposure both in the proximal and the distal (via physiologic malabsorption) small intestine (7, 23, 24). Candidate mediators include somatostatin, pancreatic polypeptide (PP), peptide YY (PYY), and glucagon-like peptide-1 (24-26).

Coordination of motility with intestinal transit of chyme

In parallel with the induction of the postprandial pancreatic response to nutrient ingestion, gastrointestinal motility is converted from a basal interdigestive state into postprandial activity (fed pattern). Evidently, motor activity determines the rates of gastric emptying and small intestinal transit of chyme; conversely, loads and sites of mucosal exposure to nutrients determine both motor and secretory responses. Thus, the coupling of motor with secretory events is an important postprandial function which serves to maintain intraluminal homeostasis. This process ensures maximal nutrient assimilation within the proximal small intestine, and economizes the effects of digestive secretions. This effect is of particular physiologic importance for the digestion of fat.

Induction, maintenance, and duration of fed intestinal motility and pancreatic secretion are coordinated (7). Postprandial motor secretory coupling is partly non-parallel, and recent observations suggest that either different intermediary mechanisms are involved or that responsiveness of motor and secretory target organs to regulatory mediators may differ or both (7).

Although under normal conditions, the site of maximal nutrient digestion and absorption is the proximal small intestine, enzymatic degradation of chyme continues during small intestinal transit, a process which is partly determined by intraluminal presence of pancreatic enzymes. For postduodenal digestion of protein and carbohydrate, not only luminal, pancreatic, but also mucosal brush-border enzymes are involved. Curiously, human pancreatic lipase is less stable than other pancreatic enzymes against acid denaturation in the duodenum (11) and during subsequent small intestinal transit, because it is rapidly destroyed by pancreatic proteases, in particular by chymotrypsin, present in chyme (7, 15, 27). This fact makes lipid digestion vulnerable in pathologic conditions.

Largely independent of the presence of intraluminal pancreatic enzymes, a significant proportion of ingested nutrient escapes luminal digestion and is delivered across the ileocecal region into the colon. Human physiologic malabsorption has been studied in most detail for carbohydrates. It usually amounts to ~10% but may range from 1% up to 30% (16, 18). Physiologic malabsorption has also been demonstrated for lipids and proteins (6, 15, 24).

Interdigestive exocrine pancreatic function

In the fasting state, characterized by the absence of stimulatory nutrients within the gastrointestinal lumen, the human pancreas is not quiescent. Outputs of water, bicarbonate, and enzymes occur in concert with the phases of interdigestive cyclical motility (migrating motor complexes) according to which they are defined and termed (4). Moreover, fasting gastric and biliary secretions are also coordinated with this cyclical interdigestive activity. During phase I, the phase of motor quiescence, secretory rates are minimal. Phase II, a phase of irregular motor activity and quantitatively the most important interdigestive phase, is associated with moderate pancreatic outputs. In humans, even within phase II the variations of motility are tightly coordinated with parallel changes in pancreatic enzyme outputs, mediated by endogenous changes in vagal-cholinergic tone (28, 29). In addition, alpha-adrenergic pathways and circulating somatostatin-28 concentrations appear to serve as inhibitory mechanisms. Phase III, a brief period of strong regular peristaltic contractions, is preceded by large pancreatic enzyme outputs (30). This concludes the cycle. In humans, the normal entire interdigestive cycle has a median duration of between 60 and 150 min. Physiologically, the tight, coupled interdigestive motor and secretory activities serve to degrade luminal debris, promote antegrade peristalsis, prevent bacterial overgrowth, and thus maintain intraluminal homeostasis even during periods of prolonged fasting.

Acute pancreatitis: physiology and patho-physiology with respect to nutrition

Approximately 75% of the patients with acute pancreatitis have a mild disease with a mortality rate well below 1% (31) as classified by the Atlanta criteria (32). Patients with mild disease may be identified early after symptom onset by the use of a single marker such as urinary trypsinogen activation peptide (TAP) (33), scoring system such as the Ranson criteria (34) or computed tomographic scanning (35). The majority of these patients can be managed with standard supportive measures that do not need special nutritional treatment; most will resume a normal diet within 3–7 days. Malnutrition may, however, aggravate the course of the disease in acute pancreatitis. In order to understand potential hazards and benefits of various forms of nutritional support, it is necessary to analyze the patterns of pancreatic secretion during acute inflammation.

During acute pancreatitis, specific and non-specific metabolic changes occur. Under the influence of inflammatory mediators and pain, the basal metabolic rate may increase leading to a higher energy consumption (36). These changes do not, however, occur in all the patients. This emphasizes the importance of direct measurement of energy expenditure using techniques such as indirect calorimetry when possible. If acute pancreatitis is complicated by sepsis, roughly 80% of the patients are in a hypermetabolic state with an increase of the resting energy expenditure (REE) (36, 37). These patients have increased nutrient requirements because of increased rates of REE and protein breakdown (36, 37). A negative nitrogen balance has been associated with an adverse clinical outcome. Net nitrogen losses are as much as 20–40 g/day in some patients with acute pancreatitis (38, 39). In one study, patients with acute pancreatitis who were in a negative nitrogen balance had a 10-fold increased mortality rate than those with a positive balance (40). It has to be stressed, however, that the relationship between nitrogen balance and outcome may simply reflect the relationship between nitrogen balance and severity of disease as none of these studies was stratified according to disease severity (41).

Protein calories malnutrition can also arise in patients with acute pancreatitis simply because they are subjected to prolonged periods (>10 days) of inadequate oral intake.

Deficiencies in certain amino acids may enhance pancreatic inflammation, leading to a potential vicious circle (42). Increased endogenous gluconeogenesis in patients with acute pancreatitis is a manifestation of the metabolic response to severe inflammation. In common with patients with sepsis or trauma this endogenous gluconeogenesis can only be partially suppressed with exogenous glucose. Finally, an increase in oxygen extraction by 20–30% indicates an enhanced energy consumption or a decreased blood supply to vital organs

due to hypovolemia or decreased cardiac performance during the inflammatory process (36).

Substrate metabolism in acute pancreatitis

Lipids

Several mechanisms have been proposed to explain how elevated serum lipids can damage the inflamed pancreas and how a deranged enzyme secretion by the organ may alter serum lipids. In the injured pancreas, capillary permeability is increased which facilitates leakage of activated pancreatic enzymes (43, 44). This may in turn promote local hydrolysis of triglycerides from chylomicrons which can exhibit local toxicity towards capillary membranes causing further damage to the pancreas.

In animal models, infusion of high amounts of triglycerides causes pancreatitis-like changes and a rise of free fatty acids in the serum. As a consequence, the formation of microthrombi is enhanced and this may aggravate the disease by causing ischemic injury to the tissue. In the majority of published human studies, intravenous lipid does not increase exocrine pancreatic secretion (45–50). If lipid is administered into the small intestine, the stimulatory effect depends largely on the anatomic site of administration. Lipid perfused into the duodenum is a powerful stimulus for exocrine pancreatic secretion. If, however, the same amount of lipid is perfused into the jejunum, then only a minimal stimulation of exocrine pancreatic secretion occurs. This minimal stimulation is not specific for lipids, but can be observed for all forms of jejunal food administration.

In conclusion, jejunal administration induces less pancreatic secretory responses than gastric or duodenal perfusion of enteral diets. This provides a theoretical rationale for jejunal administration of nutrients in patients with acute pancreatitis receiving enteral nutrition. Clinical studies confirming the benefits of jejunal administration compared to other means of enteral administration are awaited. The relative reduction in exocrine pancreatic secretion occurring with jejunal administration compared to parenteral nutrition is, at present, unknown.

Severe hyperlipidemias occur in patients with acute pancreatitis. It is not clear whether these represent an etiological factor or whether they are a consequence of the pancreatic disease, or possibly a combination of both (42, 51). In patients with hyperlipidemia, the risk for the development of pancreatitis is increased. Most prominently, hypertriglyceridemia ranging up to 80–100 mmol/l can be seen in patients with hyperlipidemia preceding pancreatitis (51). In these patients, low-fat diets which decrease serum triglycerides, may reduce the frequency of acute pancreatitis attacks. On the other hand, patients with acute pancreatitis frequently show elevated serum triglyceride concentrations (43, 52). Increases in cholesterol and free fatty acid serum concentrations have also been reported. As the acute

phase of pancreatitis subsides, serum lipids tend to return to the normal range. Adverse reactions to lipid infusions occur in less than 5% of applications (42, 53–55). However, four cases have been reported in the literature where acute pancreatitis developed after intravenous infusion of fat emulsions (56–58). Unfortunately, serum triglyceride and other lipid levels were not well documented or reported in three of these cases, while three patients had additional diseases and drug therapies.

In conclusion, gastric and duodenal perfusion of enteral diets are powerful stimulants of exocrine pancreatic secretion, whereas jejunal administration induces only a minimal pancreatic secretory response. Lipid metabolism seems to be altered in acute pancreatitis: there is a possibility of enhanced organ damage through high concentrations of serum triglycerides. The mechanism of altered lipid metabolism is not entirely clear (altered lipid oxidation? lipid clearance?). Pancreatic secretion is not stimulated by intravenous lipid, while the anatomic site of nutrient administration determines the degree and extent of pancreatic stimulation after enteral nutrient application. Overall there is no proven causal relationship between infusion of exogenous fat and the development of pancreatitis. There is therefore no firm evidence to contraindicate the use of long chain triglycerides or other fats in patients with acute pancreatitis provided these patients are monitored for hypertriglyceridemia.

Proteins and amino acids

As noted before, a negative nitrogen balance has been associated with a poor clinical outcome in severe forms of acute pancreatitis. The major objectives of nutrition in these patients is to minimize protein losses (40). It is important to compensate the increased protein turnover. The pancreas itself requires an appropriate supply of amino acids as it synthesizes significant amounts of protein. As for lipid administration, jejunal perfusion of elemental diets containing defined amounts of protein or amino acids is well tolerated and does not stimulate exocrine pancreatic secretion. In contrast, gastric and duodenal perfusion of proteins are potent stimulants of pancreatic secretory responses. An added benefit for elemental diets for putting the pancreas at rest and reducing exocrine secretion compared to standard diets with intact protein was shown in several studies (59). Regardless of whether the elemental diet was ingested orally, infused into the duodenum, or into the jejunum, the elemental diet resulted in less stimulation than the standard diet infused at the same level (49, 60–66). Finally, intravenous administration of protein hydrolyzates either inhibit exocrine pancreatic secretory responses or they do not have any effect (67, 68).

In conclusion, there is an increased protein catabolism in severe acute pancreatitis. Amino acids, when given parenterally, do not stimulate the exocrine pancreas

directly, while the anatomic site of protein and amino acids administration determines the degree and extent of pancreatic stimulation during enteral nutrition. Elemental diets are regarded as the most beneficial diets for patients with pancreatitis. Intravenously applied amino acids stimulate gastric acid secretion which may stimulate itself in the duodenum, pancreatic secretion.

Carbohydrates

Beside fat, carbohydrates, mainly glucose, are important sources of energy. Carbohydrates are a preferred energy supply in acute pancreatitis for several reasons: (1) Carbohydrates can be easily supplied; (2) glucose supply counteracts in part with the intrinsic gluconeogenesis from protein degradation, thus helping to reverse in part deleterious and unwanted protein catabolism; (3) energy supply in the form of carbohydrates instead of lipids as the main source of calories reduce the potential risk of hyperlipidemia but this cannot be completely avoided. There is a physiological maximum to the rate of glucose oxidation (~ 4 mg/kg/min) and provision of glucose in excess of this is wasteful both in terms of lipogenesis and glucose recycling, but is also dangerous because it results in hyperglycemia and hypercapnia. Similar to lipid and protein administration, intravenous glucose does not stimulate exocrine pancreatic secretion (68–70). The main risk with intravenous glucose in acute pancreatitis is hyperglycemia. Insulin release is also frequently impaired in patients with acute pancreatitis rendering the patient susceptible to develop hyperglycemia; overt diabetes may occur and this represents a risk factor for long-term survival. Hyperglycemia following glucose infusion can only partly be corrected with exogenous insulin administration. There is little evidence that supplemental insulin is beneficial to the patient in any other form than monitoring blood glucose levels.

Finally, enteral glucose perfusion into the jejunum in is the weakest stimulus for exocrine pancreatic secretory responses (66). It is weaker than intragastric or intraduodenal but this cannot be concluded with certainty with regard to a comparison of parenteral nutrition.

In conclusion, glucose metabolism in acute pancreatitis is determined by an increase in energy demand. Intravenous administration of high doses of glucose carries the risk of hyperglycemia as the insulin response is often impaired. The insulin resistance can be corrected only in part by exogenous insulin administration and this corrective therapy does not appear to bear an additional risk for the inflamed pancreas.

Consequences for nutritional support

In the past two decades, increasing interest has developed in defining the role of nutritional support in the management of patients with acute pancreatitis.

The most controversial topics include the route of nutrient delivery (parenteral vs. enteral), the composition of substrates (are lipids safe?, if so, which forms of lipids?), and finally whether nutritional strategies are a therapeutic intervention or simply a supportive therapy.

As summarized before, many beliefs are derived from physiological studies and are not supported by evidence from prospective clinical trials. In fact, very little controlled, prospective data are available which would form the basis for guidelines related to the route of nutrient delivery, the composition of substrate, and the role of nutrients in the management of these patients. In the last six years, the picture has changed with respect to the route of nutrient delivery. Several prospective, controlled trials provide evidence that jejunal feeding is possible and safe, but the evidence that it is effective or beneficial remains tenuous.

Parenteral nutrition in acute pancreatitis is useful as an adjunct in the nutritional maintenance of the patients. A reduction in mortality has been claimed with improved nutritional status, especially in patients with moderate or severe forms of acute pancreatitis. On the other hand, patients with acute pancreatitis who receive parenteral nutrition have been shown to have an increased rate of catheter-related sepsis and to have metabolic disturbances such as hyperglycemia (1, 40, 41, 71). Here we have to keep in mind, that both catheter-related sepsis and hyperglycemia are often the consequence of overfeeding rather than consequences of the mode of nutritional support itself (72). Finally, it has been mentioned that prolonged parenteral nutrition may suppress the immune system, promote gastrointestinal leakage by a loss of intestinal mucosal barrier with the potential risk of subsequent bacterial translocation. This is a theoretical risk, but a number of recent reviews have concluded that there is no evidence to support this thesis (73).

Energy requirements

The reduction in the ingestion of food together with an increased demand in patients with severe pancreatitis often results in a negative energy balance with the potential of development of malnutrition. In an analogy to patients with sepsis, patients with acute severe pancreatitis are hypermetabolic, have a non-suppressible gluconeogenesis despite sufficient caloric intake, an increased ureagenesis and an accentuated net protein catabolism which can go up to 40 g nitrogen/day. As stated above, glucose supply cannot inhibit intrinsic gluconeogenesis and states of acute catabolism completely. The more Ranson's prognostic signs are present, the more excessive is hypermetabolism. REE is variable in patients with pancreatitis which range from 77% to 139% of predicted energy expenditure (37). REE is significantly higher in patients with pancreatitis complicated by sepsis or multiorgan failure (MOF) (37, 38).

In one study, an REE up to 158% of predicted REE was measured (37). Therefore, septic complications are important factors influencing REE in acute pancreatitis. In these cases, the Harris–Benedict equation is an unreliable estimate of caloric expenditure and indirect calorimetry is recommended.

Energy supply

In severely ill patients, neither hypercaloric nor isocaloric nutritional support can prevent protein catabolism. In contrast, both enhance the metabolic burden as measured by energy expenditure, thermogenesis, urea production rate, glucose and lactate levels (36, 74). A hypocaloric energy supply of ~15–20 kcal/kg/day is therefore more suitable during the early catabolic stage of non-surgical patients with MOF (74). The goal of 1.2–1.5 g/kg/day of protein intake is optimal for most patients with acute pancreatitis (33). Although there is an increased urea production rate in patients receiving a high protein diet (more than 1.5 g protein/kg/d), this regimen might ensure that a positive protein balance can be achieved (74). Based on this information, a high protein intake should be given to patients with only a severe negative nitrogen balance (e.g. measured by urinary urea excretion), but a high protein intake that is given to patients with severe acute pancreatitis with a severe negative nitrogen balance is still tenuous.

If the course of the disease is complicated by an MOF syndrome, then the calorie and protein requirements have to be adapted. Lower protein loads ~1.2 g/kg/day should be given to patients with renal or hepatic failure. Monitoring urinary urea excretion may help to meet actual nitrogen requirements.

Patients with pancreatitis appear to have an impairment in their capacity for net protein synthesis. Similar to septic patients, patients with severe pancreatitis are less sensitive to the protein-sparing effects of glucose infusion than normal volunteers and reveal an accelerated protein breakdown (36).

The impaired glucose oxidation rate cannot be normalized by insulin administration or by increasing glucose administration. Normally, the blood glucose levels should not exceed 10 mmol/l. Insulin doses higher than 4–6 units/h should be avoided.

It is important to attempt to deliver the caloric need by enteral route. This, however should be determined by patient tolerance. If the enteral supply is inadequate, then the rest should be given parenterally. When enteral nutrition is impossible total parenteral nutrition should be started.

Total parenteral nutrition in acute pancreatitis

Total parenteral nutrition has been the standard treatment for providing nutrients to patients with severe acute pancreatitis. The concept behind this strategy was two-fold: firstly, to avoid stimulation of exocrine

pancreatic secretory responses ('to put the pancreas at rest') and secondly, to improve the nutritional status of the patient. The evidence in favor of intravenous feeding is, however, not supported by clinical trials. Two clinical prospective studies have been performed on the use of parenteral nutrition in acute pancreatitis (71, 75). The study of McClave et al. (71) compared nasojejunal feeding with total parenteral nutrition showing no difference on the outcome but the costs for enteral nutrition was four times lower. In the study of Sax et al. (75), intravenous feeding was compared with no nutritional support. The results demonstrated that intravenous nutrition did not affect the outcome of patients with mild-to-moderate pancreatitis as defined by complication rate, days of oral food intake, or by the total hospital stay. However, an increase in catheter-related infections was observed in the patients receiving total parenteral nutrition. These data indicate that total parenteral nutrition is associated with certain disadvantages. Besides the increased risk of catheter-related sepsis, severe hyperglycemia and other metabolic disturbances have been reported. It is clear, therefore, that overfeeding is a major risk factor for complications in patients receiving parenteral nutrition. In recent years, more concern has been expressed about the possibility of parenteral nutrition adversely affecting gut barrier function. Whilst there is more evidence to support this hypothesis in animals there is tenuous little evidence in clinical practice (73).

Is early enteral nutrition dangerous in acute pancreatitis?

The gastrointestinal tract is increasingly seen as a potential source for systemic inflammatory responses (SIRS) with the possibility of clinical progression to sepsis, MOF, and death (76). This seems to be most common in a metabolically deprived gut (77, 78). These observations have led to the concept of mucosal injury which has also been invoked in experimental acute pancreatitis (79). Parallel to this concept, several studies have shown that septic complications can be reduced when the patients received early enteral feeding; these studies were carried out patients with trauma, thermal injury, and major gastrointestinal surgery (80, 81).

Today, early enteral nutrition is considered an important mode of acute therapy in critically ill patients, not only to reduce catabolism and loss of lean body mass, but also to modulate the acute phase response and preserve visceral protein metabolism with the potential to downregulate the splanchnic cytokine responses (82). All these effects should help to maintain the structure and function of the gastrointestinal tract. Based on this information, several prospective, randomized clinical trials have been performed in the past few years comparing early enteral with parenteral nutrition in patients with acute pancreatitis. McClave et al. (71) conducted the first prospective trial in patients with

mild-to-moderate acute pancreatitis. Patients were randomized either to total parenteral nutrition or to total enteral feeding via a nasojejunal tube, with both groups receiving isocaloric, isonitrogenous nutrition within 48 h after admission to the hospital. The first conclusion which can be drawn from the study is that enteral feeding in acute pancreatitis is possible. The outcome in the study revealed no statistical differences in infectious complications, length of intensive care unit stay, length of hospital stay, or days of oral food intake. Patients on intravenous feeding had significantly higher glucose concentrations in the first five days; it should be noted that only 82% of the patients with enteral feeding reached their caloric goal compared to 96% of patients on total parenteral nutrition. The study has formed the basis for several additional trials despite the fact that it has one severe limitation: the study was done in patients with mild-to-moderate acute pancreatitis who normally recover within a few days and who may not require any nutritional support. Almost parallel to McClave's paper, a second study by Kalfarentzos et al. (83) was published which was performed in patients with severe necrotizing acute pancreatitis. Patients were prospectively randomized to either enteral feeding through a nasoenteric tube with a semi-elemental diet or to intravenous feeding within 48 h of admission. Enteral feeding was well tolerated without adverse effects on the course of the disease. More importantly, patients who received enteral feeding experienced fewer septic complications and fewer total complications compared to those receiving parenteral nutrition. Finally, the costs of nutritional support were three times higher in the patients receiving intravenous nutrition. In a further study by Windsor et al. (82), parenteral nutrition was compared to enteral nutrition; the authors were able to show that enteral nutrition attenuates the acute phase response in acute pancreatitis and improves disease severity and clinical outcome despite the fact that the pancreatic injuries were virtually unchanged on CT scan. Enteral feeding modulated, however, the SIRS and sepsis resulting in a beneficial clinical outcome (APACHE II-Score and C-reactive protein). Unfortunately, in this study only a few patients had severe pancreatitis and the total amounts of nutrient received, revealed marked differences between the enteral and parenteral groups. The differences observed may therefore be a consequence of the amounts of nutrients received and not necessarily the mode of nutritional support. Another study from Powell et al. (84) could not confirm the data on the inflammatory response in patients with prognostically severe acute pancreatitis.

The implications of these studies are important and contrary to current recommendations: (1) enteral feeding is possible but prescribed intakes of nutrients are frequently not achieved (85); (2) nasojejunal tubes are feasible and desirable in the management of patients with acute pancreatitis but their placement is sometimes

difficult without the endoscopic help; (3) despite the heterogeneity of patients with acute pancreatitis there is some evidence that enteral feeding may improve disease severity and clinical outcome in patients with severe disease. However, additional data from large, randomized, controlled trials are necessary to confirm this contention (41); (4) enteral feeding is usually considered less costly than parenteral nutrition but this may not always be the case if morbidity related to feed delivery is taken into account (85); and (5) the presence of complications (pancreatic ascites, fistula formation or fluid collection) is not a contraindication to enteral feeding.

Many patients with severe necrotizing pancreatitis may develop a prolonged paralytic ileus precluding complete enteral nutrition. In these patients, it is still possible to administer small amounts of enteral nutrition particularly if double or triple lumen tubes are used. Pseudocysts and other complications of acute necrotizing pancreatitis are no contraindication for enteral feeding, although it has to be stated that the data basis is insufficient to give strong recommendations.

Oral refeeding after acute pancreatitis

Oral refeeding can be started when pain is controlled and the pancreatic enzymes return to normalcy (86). Unfortunately, not enough information is available on the optimal timing of refeeding nor on the optimal form of diet.

In general, patients are refeed with small amounts of a carbohydrate-protein diet; the number of calories are gradually increased with careful supplementation of fat over a period of 3–6 days. In one study, the frequency of recurrent pain and the associated risk factors during refeeding was defined in patients with acute pancreatitis (86). Twenty-one percent of patients had pain relapse episodes during oral refeeding. In half of these patients the pain occurred on days one and two. Patients with a serum-lipase concentration three times higher than those of the upper limit and with a higher CT-Balthazar-score had pain relapses more often.

Conclusions and recommendations

The past clinical emphasis on the need for 'gut rest' in order to decrease pancreatic stimulation has to be revised. The nutritional management of patients with acute pancreatitis is now guided by four main principles:

- (1) the altered metabolism should be corrected by an adequate nutrient supply;
- (2) to avoid iatrogenic complications (particularly those related to overfeeding);
- (3) to reduce pancreatic stimulation to subclinical levels (whether this is an important factor, remains to be demonstrated); and
- (4) to attenuate the overall SIRS.

Aggressive nutritional support (enteral or parenteral) is not required for mild-to-moderate forms of acute pancreatitis (the majority of patients).

Conclusion I

Nutritional support in mild-to-moderate pancreatitis:

- There is no evidence that either enteral or parenteral nutrition has a beneficial effect on clinical outcome in patients with mild-to-moderate pancreatitis;
- If this is also true in patients with preexisting malnutrition it is not known;
- Nutritional therapy has to be considered earlier if refeeding is delayed.

Recommendation I

Nutritional treatment in mild and moderate pancreatitis:

1. Step — fasting
(2–5 day) — treat the cause of pancreatitis
— analgesics
— i.v. fluid and electrolyte replacement
↓
2. Step — refeeding
(3–7 day) — diet — rich in carbohydrates
no pain — moderate in protein
enzymes regredient — moderate in fat
↓
3. Step — normal diet

The use of early enteral feeding in patients with severe disease decreases, however, the incidence of nosocomial infection, reduces the duration of SIRS and decreases the overall disease severity. Decisions involved in nutritional management are therefore driven by the disease severity. Greater severity of the disease dictates the need for nutritional support and predicts those patients with acute pancreatitis which most likely will benefit from nutritional therapy. Several factors remain to be clarified: optimal timing of nutritional therapy, route of administration (jejunum or duodenum? stomach?) or parenteral and nutrient formulation remain uncertain at present due to the lack of controlled clinical trials in order to define optimal nutritional therapy. It is clear, however, that enteral feeding is safe; jejunal tubes are well tolerated without an exacerbation of pancreatitis-related symptoms (71, 87–89). When the caloric goal with enteral nutrition is not possible, parenteral nutrition should be used. The administration of fat is also safe when hypertriglyceridemia (>12 mmol/l) is avoided.

The consensus group agrees that there is good evidence to start nutritional therapy in patients with

severe pancreatitis with enteral jejunal approach but we have to keep in mind that parenteral nutrition is an alternative method, when enteral nutrition is inadequate. The essence of successful nutritional support is to use those techniques which the patients tolerates and which are seen to be associated with minimal morbidity.

Conclusion II

Nutritional support in severe pancreatitis:

- Nutritional support is essential in patients with severe disease.
- The route of nutrient delivery (parenteral/enteral) should be determined by patient tolerance. Enteral should be attempted in all patients. The clinician should monitor intakes carefully to ensure adequate nutritional support. Many patients will require a combination of enteral and parenteral nutrition.
- Many beliefs are derived from physiological studies and are not supported by evidence from prospective trials.
- Very little controlled, prospective data are available that could form the basis for evidence-based guidelines.

Recommendation II

Nutritional therapy in severe pancreatitis:

- Patient with severe disease, complications or need for surgery require early nutritional support to prevent the adverse effects of nutrient deprivation (enteral and/or parenteral nutrition is possible according to the patient condition):
 - Some authorities recommend early jejunal feeding with an elemental diet and others the parenteral nutrition with concomitant enteral given to tolerance;
 - When side effects occur or the caloric goal cannot be achieved, enteral nutrition should be combined with parenteral nutrition.
- The combined approach allows to reach the nutritional goals most of the time.
- The use of intravenous lipids as part of parenteral nutrition is safe when hypertriglyceridemia (>12 mmol/l) is avoided.

Recommendation III

Nutrient requirements:

- energy ~25–35 kcal/kg BW/day;
- protein 1.2–1.5 g/kg BW/day;

- carbohydrates 3–6 g/kg BW/day corresponding to blood glucose concentration (aim: <10 mmol/l);
 - lipids up to 2 g/kg BW/day corresponding to blood triglyceride concentration (aim: <12 mmol/l):
- When nutritional support is necessary, start with enteral feeding by a jejunal feeding tube (when the caloric goal cannot be reached, give additional parenteral support);
- When enteral nutrition is not possible (e.g. prolonged paralytic ileus), combine parenteral nutrition with a small content of an elemental or immuno-enhancing diet (10–30 ml/h) continuously perfused to the jejunum.

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