

# Nutrition in acute pancreatitis

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## Abstract

The management of acute pancreatitis depends on the evaluation of its severity, mainly based on multiparameter scores such as Ranson score. Patients with mild or moderate acute pancreatitis are characterized by a spontaneous recovery and do not require enteral or parenteral nutrition. Patients with severe pancreatitis need a nutritional support. According to present data, enteral nutrition should be preferred to parenteral nutrition. Parenteral nutrition should be used in cases with prolonged ileus, when patient do not tolerate enteral nutrition and when enteral nutrition is not unable to satisfy nutritional requirements. Energy requirements vary between 25 and

35 kcal/kg/day. It is recommended to start with 15 to 20 kcal/kg/day in patients with multi-organ failure. Glucose supply should be 3 to 6 g/kg/day, if necessary associated with insulin in order to maintain blood concentrations < 10 mmol/l. Fat is well tolerated in the absence of hypertriglyceridemia. As in other stress conditions, a fat supply representing 30% of non-protein energy has been recommended. Protein requirements have been estimated at 1.2-1.5 g/kg/day. Vitamins and trace-elements should be integrated to nutritional support during severe pancreatitis with special attention to vitamins A, C, E, zinc and selenium.

**Keywords:** acute pancreatitis, nutrition, enteral nutrition, parenteral nutrition

## Introduction

The prevalence of acute pancreatitis has been estimated to 0.7 new case per 1,000 habitants/year in western countries [1]. Oedematous pancreatitis represents 70% of all cases and is associated with uneventful recovery [1-3]. Necrotizing pancreatitis occurs in 30% of patients and is responsible for a 30% mortality rate. Early deaths during acute pancreatitis are usually due to deteriorated underlying health status or to organ failure. Late deaths are usually related to infected necrosis [4]. Several consensus groups recently addressed the management of acute pancreatitis and particularly its causes and pathogenesis, diagnosis, evaluation of severity, and treatment [5-7]. The present paper mainly concerns nutritional consequences of acute pancreatitis and nutritional support, which is now recognized as a key element in the treatment of severe acute pancreatitis [4,7].

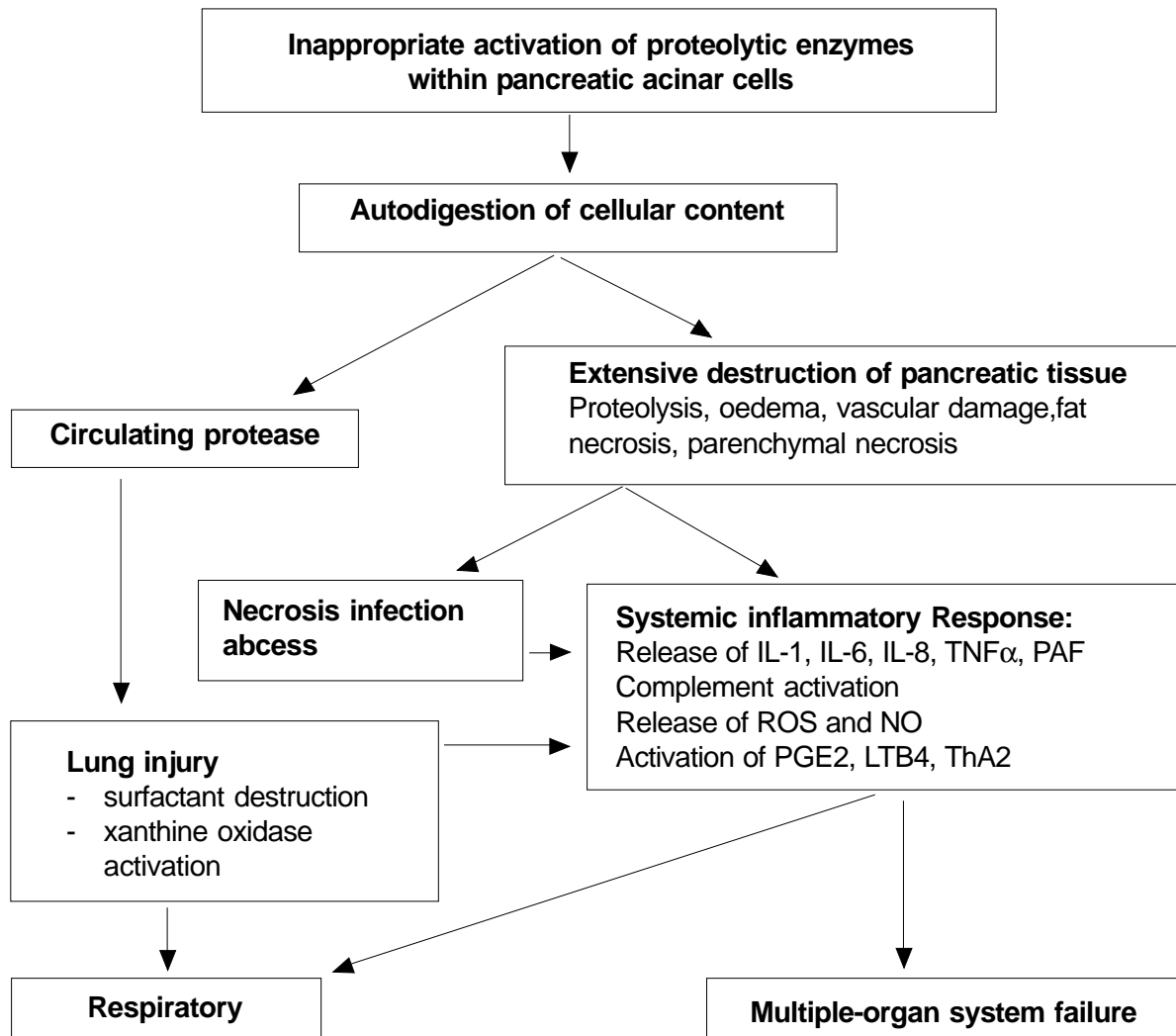
## Causes and pathogenesis of acute pancreatitis

Biliary lithiasis, ethanol abuse and idiopathic pancreatitis represent the main causes of acute pancreatitis. Less commonly endoscopic retrograde cholangiopancreatography, hyperlipidemia, drugs, pancreas divisum, abdominal trauma and, rarely, hereditary pancreatic disease can be responsible for acute pancreatitis [1]. The pathogenesis of acute pancreatitis is summarized in **Figure 1**. The inappropriate activation of proteolytic enzymes is considered as the first step in the development of pancreatitis. Recently, the hydrolysis of an N-terminal peptide, called trypsinogen-activating peptide, has been shown to induce trypsinogen molecule activation within the acinar cell [2]. In normal conditions, trypsin inhibitors such as serine protease inhibitor Kasal type 1, protects pancreatic tissue against auto digestion. Alterations of the mechanisms of prevention of pancreatic cell autodigestion have been reported in some cases of idiopathic and hereditary pancreatitis [2]. During acute pancreatitis, the auto digestion of pancreatic acinar cells content leads to the ap-

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**FIGURE 1.** THE INAPPROPRIATE ACTIVATION OF PROTEOLYTIC ENZYMES IS CONSIDERED AS THE FIRST STEP IN THE DEVELOPMENT OF PANCREATITIS. DURING ACUTE PANCREATITIS, THE AUTO DIGESTION OF ACINAR CELLS CONTENT LEADS TO THE APPEARANCE OF CIRCULATING PROTEASES, RESPONSIBLE FOR EARLY PULMONARY DAMAGE. MOREOVER, LOCO-REGIONAL RELEASE OF PROTEASES RESULTS IN AN EXTENSIVE NECROSIS OF PANCREATIC TISSUE. EXTENSIVE TISSUE NECROSIS IS RESPONSIBLE FOR A SYSTEMIC INFLAMMATORY RESPONSE SYNDROME, CHARACTERIZED BY AN ACTIVATION OF IMMUNE CELLS AND BY THE RELEASE OF INFLAMMATORY MEDIATORS, WHICH CAN INDUCE MULTI-ORGAN SYSTEM FAILURE. ROS MEANS REACTIVE OXYGEN SPECIES; NO, NITRIC OXIDE, IL, INTERLEUKIN; TNF, TUMOR NECROSIS FACTOR; PAF, PLATELET ACTIVATING FACTOR; PG, PROSTAGLANDIN; LT, LEUCOTRIEN; TH, THROMBOXAN.

pearance of circulating proteases, which can induce early pulmonary damage [2]. Moreover, loco-regional release of proteases results in an extensive necrosis of pancreatic tissue. Extensive tissue necrosis is responsible for a systemic inflammatory response syndrome (SIRS) which is characterized by an activation of immune cells and for the release of inflammatory mediators such as interleukin-1, TNF  $\alpha$ , platelet activating factor, reactive oxygen species, nitric oxide, PGE2 and LTB4. SIRS, which constitutes the initial phase of severe pancreatitis, can result in multi-organ system fail-

ure. Future therapies for acute pancreatitis may include antagonists of inflammatory mediators such as interleukin 1, TNF  $\alpha$  and platelet activating factors [2]. The secondary evolutive phase of pancreatitis is characterized by the occurrence of local complications. The infection of necrosis is a key element of the prognosis of acute pancreatitis: infected necrosis represents 30 to 70% of necrotizing pancreatitis and accounts for 80% of deaths [1]. The similarity of bacterial flora found in infected necrosis with gut flora argues for the intestinal origin of necrosis infection [4].

## Evaluation of the severity of acute pancreatitis

Severe acute pancreatitis is characterized by the occurrence of organ failures and/or local complication such as necrosis infection [6]. The evaluation of grade of severity is of importance for patient management and particularly for the decision to transfer patients to intensive care units. Several uni and multiparameter indicators have been proposed [8-11]. The parameters considered of interest by the French consensus were [6]:

- underlying patient status (age > 80 y, body mass index > 30, preexisting organ insufficiencies);
- specific scores (Ranson [8] or Imrie [9], **Tables 1**) > 3;
- organ function assessment including hemodynamic (heart frequency, arterial pressure < 90 mm Hg despite fluid infusion, peripheral circulation), respiratory (respiratory frequency, 5 PaO<sub>2</sub> in room air < 60 mm Hg), neurologic (altered consciousness, Glasgow score < 13), renal (urine output, plasma creatinine > 170 μmol/l), and hematologic criteria (platelet count < 80,000/ml). These non specific criteria make it possible to ensure a continuously monitoring;
- C-reactive protein (CRP) > 150 mg/l after 48 hours. CRP increase is frequently the reflect of local complications;
- Tomodensitometry Balthazar index [10] > 3 (**Table 2**).

TABLE 1. Ranson and Imrie scores [8,9].

Ranson score (one point / item)	Imrie score (one point / item)
<p>At admission:</p> <ul style="list-style-type: none"> <li>- Age &gt; 55 y.</li> <li>- White-cell count &gt; 16,000 /ml</li> <li>- Blood glucose &gt; 10 mmol/l (excepted in diabetics)</li> <li>- serum LDH &gt; 350 U/L (1,5 N)</li> <li>- serum AST &gt; 250 U/L (6N)</li> </ul> <p>After 48 hours:</p> <ul style="list-style-type: none"> <li>- Absolute hematocrite decrease &gt; 10 %</li> <li>- Blood urea nitrogen increase &gt; 1,8 mmol/l</li> <li>- Serum calcium &lt; 2 mmol/L</li> <li>- PaO<sub>2</sub> &lt; 60 mm Hg</li> <li>- Base deficit &gt; 4 mmol/l</li> <li>- Fluid sequestration &gt; 6 l</li> </ul>	<ul style="list-style-type: none"> <li>- Age &gt; 55 y.</li> <li>- White cell count &gt; 15,000 /ml</li> <li>- Blood glucose &gt; 11 mmol/l (excepted in diabetics)</li> <li>- Serum LDH &gt; 600 U/L (3,5 N)</li> <li>- Blood urea &gt; 16 mmol/L</li> <li>- Serum calcium &lt; 2 mmol/l</li> <li>- PaO<sub>2</sub> &lt; 60 mm Hg</li> <li>- Serum albumin &lt; 32 g/L</li> <li>- Serum AST &gt; 100 U/L (2N)</li> </ul>

TABLE 2. Tomodensitometry Balthazar score [9].

Pancreatic and peripancreatic inflammation	Pancreatic necrosis	
<p>Grade A : normal pancreas (0 pt)</p> <p>Grade B : focal or diffuse pancreas enlargement (1 pt)</p> <p>Grade C : pancreas heterogeneity + peripancreatic fat densification (2 pts)</p> <p>Grade D : peripancreatic necrosis (3 pts)</p> <p>Grade E : multiple peripancreatic necrosis or presence of gas within necrosis (4 pts)</p>	<p>No necrosis (0 pt)</p> <p>Necrosis &lt; 30 % (2 pts)</p> <p>Necrosis 30–50 % (4 pts)</p> <p>Necrosis &gt; 50 % (6 pts)</p>	
Severity index	Morbidity %	Mortality %
< 3	8	3
4-6	35	6
7-10	92	17

Apache II score (" 8) ability to detect severe pancreatitis is similar to that of specific scores > 3. The occurrence of an organ failure during the first 48 hours indicates the need for intensive care unit. After 48 hours, patients at risk can be defined by a Ranson or Imrie score > 3, CRP > 150 mg/l or Balthazar score > 3.

## Effects of nutritional support on pancreatic secretion

In normal conditions, pancreatic secretions are characterized by four phases: the basal phase, which corresponds to the post absorptive condition; the cephalic phase during which the pancreatic secretion is stimulated through vagal ways by food sight, smelling and taste; the gastric phase, due to gastric distension and gastrin secretion; and the intestinal phase, stimulated by the presence of food in the duodenum and jejunum, and mediated by cholecystokinin and secretin. Pancreatic secretion is influenced by the composition of meals: amino acids, proteins and fat are responsible for the secretion of trypsin and lipase mediated by cholecystokinin; carbohydrates induce amylase secretion; a mixed meal of 20 kcal/Kg induces the maximal enzyme output. Physical properties of the meal also influence the enzyme output: solid meals induce a longer response than liquid and homogenized meals [7].

It must be underlined that data on the effects of enteral nutrition (EN) on pancreatic secretion were obtained in healthy subjects and do not reflect the pancreatic response to nutrients during acute pancreatitis. As a matter of fact, one study conducted in patients with acute pancreatitis showed an impairment of nutrient-stimulated trypsin and lipase secretion [12]. The pancreatic response to EN depends on the site of infusion and on the characteristics of the infused nutrients. Intra-gastric or duodenal infusion of fat and proteins is responsible for the highest enzyme output [7]. Jejunal infusion of fat and entire proteins results in a minimal stimulation. Independently of the site of infusion, elemental diets result in less stimulation of enzyme secretion [13,14]. Total parenteral nutrition (TPN) was reported to be more effective than intraduodenal elemental diet in reducing pancreatic secretion. Surprisingly, in this study, elemental diet was a more potent stimulant of enzyme output than polymeric diet [15]. From these data on EN effect on pancreatic secretion, one can conclude that the jejunal infusion of elemental or semi-elemental diets is suitable for putting pancreas at rest. Intravenous glucose was shown to decrease pancreatic enzyme secretion in several studies. Such an effect was attributed to hyperosmolarity [16,17]. Intravenous fat emulsions were shown not to influence

pancreatic secretion. One study reported a stimulation of pancreatic enzyme secretion by the intravenous infusion of amino acid and fat [18]. Further studies showed that intravenous protein hydrolyzates and amino acids did not stimulate pancreatic enzyme secretion [13,19-21]. It is now admitted that TPN as a whole does not stimulate pancreatic enzyme secretion [3,7].

## Metabolic and nutritional consequences of acute pancreatitis

Metabolic disorders during acute pancreatitis have been recently reviewed [3,4,7]: they are characterized by a hyper metabolic and hypercatabolic status [22]. The release of inflammatory mediators, together with pain, often increases energy expenditure. Because such an increase in energy consumption is not present in all patients, a direct measurement of energy expenditure using indirect calorimetry, when possible, can be useful. In six patients operated for severe acute pancreatitis energy expenditure represented 1.49 times (range: 1.08-1.78) the predicted resting energy expenditure according to the Harris-Benedict equation. [23]. In a larger series, an increase in energy expenditure was found in 52% of patients with necrotizing pancreatitis [24] and 80% of patients with associated sepsis [24]. An increase in oxygen extraction has been reported traducing either the increase in energy demand and/or a decrease in cardiac output [22].

Abnormalities in carbohydrate metabolism are mainly due to the increases in plasma cortisol and epinephrine and subsequent insulin resistance, increased gluconeogenesis and decreased glucose oxidation. In the absence of preexisting diabetes, glucose intolerance is considered as a factor of severe prognosis [25]. However, carbohydrate supply in patients with acute pancreatitis offers several advantages [7]: carbohydrate can be easily supplied; glucose counteracts in part the increase in gluconeogenesis from protein degradation; carbohydrates given instead of fat reduce the risk of hyperlipidemia; enterally given carbohydrates are the weakest stimulus for pancreatic secretion. Glucose supply should not exceed the maximum physiological rate of glucose oxidation (approximately 4 mg/kg/min, i.e. 5.75 g/kg/day) [7]. Glucose intolerance can be partly corrected by insulin therapy in order to maintain blood glucose < 10 mmol/l.

Severe hyperlipidemia increases the risk for the development of pancreatitis [26]. On the other hand, acute pancreatitis is associated with alterations of fat metabolism. Besides the increase in lipolysis and lipid oxidation, acute pancreatitis can be accompanied by a decrease

in triglyceride clearance with hypertriglyceridemia [27]. Increases in serum cholesterol and free fatty acids can also be observed. Intravenous lipid emulsions do not stimulate pancreatic secretion and are usually well tolerated. It has been recommended that fat emulsion supply should not exceed 1 g/kg/day and be associated with a monitoring of serum triglycerides in order to avoid overpassing 2 g/l (2.5 mmol/l) [4].

During acute pancreatitis, hypermetabolism is associated with negative nitrogen balance. Net nitrogen losses reaching 20-40 g per day have been observed [23]. Proteolysis can be increased by 80% as compared with normal controls. Alanine and glutamine release by muscle is increased. Plasma amino acids are characterized by a decrease in branched-chain and gluconeogenic amino acids, mainly alanine, glutamine, serine and threonine [28,29]. The production of reactive oxygen species (ROS) production during acute pancreatitis is correlated with the mortality risk [30]. ROS and peroxidation reaction are implicated in the early phase of acute pancreatitis. Low serum levels of vitamins A, C, E and selenium during acute pancreatitis suggest a decrease in anti-oxidant defenses [30].

## **Effect of nutritional support during acute pancreatitis**

### **Effect of parenteral nutrition**

Due to its ability to ensure pancreatic rest and to improve nutritional status, TPN has been the standard way for feeding patients with severe acute pancreatitis. However, only one randomized controlled study on the effects of TPN on patients with acute pancreatitis has been carried out [31]. This study involved 54 patients with moderate acute pancreatitis (Ranson score = 1) and compared the early administration of TPN with conventional therapy including fluid resuscitation, analgesia and gastric decompression. The group receiving TPN exhibited a longer length of hospitalization and a higher rate of catheter sepsis (10.5% vs. 1.5%,  $p = 0.003$ ). The authors concluded that TPN was not useful in patients with acute pancreatitis. Unfortunately, no randomized controlled study addressed the effect of TPN in severe acute pancreatitis. Numerous non-randomized studies have been published and recently reviewed [3,4,7]. Several among these studies addressed the tolerance of fat emulsions and concluded that they were well tolerated. Some other studies reported high rates of catheter sepsis. Recent data from Zazzo showed that the prevalence of catheter infection was similar in patients with acute pancreatitis and in other intensive care

patients [4]. Two studies addressed the interest of glutamine-enriched TPN. In a randomized study of 14 patients with severe acute pancreatitis, a glutamine-enriched TPN, as compared with isonitrogenous and isocaloric TPN, improved lymphocyte proliferation, increased T-cell DNA synthesis and decreased the release of IL-8 [32]. More recently, in a similar study in 28 patients, glutamine-enriched TPN was associated with a significant decrease in the duration of TPN and a non-significant reduction of hospitalization length ( $p = 0.07$ ) [33]. The effects of two lipid emulsions, LCTs (Long chain triglycerides) and LCT/MCT (medium chain triglyceride) mixture, were compared in one cross-over prospective trial including nine patients with acute pancreatitis and acute respiratory distress syndrome (ARDS). LCT infusion increased the mean pulmonary artery pressure and pulmonary venous admixture, and decreased PaO<sub>2</sub>/FIO<sub>2</sub> ratio. As compared to LCT, LCT/MCT emulsion increased oxygen consumption, cardiac output and CO<sub>2</sub> production suggesting that LCT/MCT mixtures may be recommended in cases of acute pancreatitis and ARDS, even though infusion over a short period increases the metabolic demand [34].

### **Effect of enteral nutrition**

The usual presences of gastric intolerance in patients with acute pancreatitis, together with data on the effects of enterally given nutrients on pancreatic secretion, argue for the jejunal infusion of EN. Jejunal tube can be inserted using several methods: radiological guidance, endoscopic placement, transnasal endoscopic placement using a guide wire, self-propelling 10 spiral distal or weighted tubes. Successful insertion rates of 93% were reported using radiological guidance, 90% using endoscopic placement [35], and 75 % with self-propelling tubes [36].

Only one randomized controlled study compared EN to conventional treatment without nutritional support in 27 patients with severe acute pancreatitis. This study did not show any beneficial effect of EN on CRP, interleukin-6, TNF  $\alpha$ , morbidity and mortality [37]. Several non-randomized reported the good tolerance of jejunal feeding and suggested its beneficial effect [3,4,7]. A prospective randomized study, stratified on severity score, was performed in 30 patients with acute pancreatitis undergoing jejunal nutrition. One group received a semi-elemental diet ( $n = 15$ , 35 kcal/kg/d) and the other group an isocaloric polymeric diet ( $n = 15$ ). The semi-elemental group was characterized by a more frequent improvement of Dxylose absorption, a reduction of length of stay in hospital and a lesser weight loss. These data suggest

that semi-elemental nutrition allows better clinical outcome and maintenance of digestive trophicity [38]. The possible interest of probiotics for preventing sepsis from intestinal origin was recently pointed: a randomized controlled study in 45 patients showed that the addition of lactobacillus plantarum and fiber supplement to EN induced a decrease in the infection rate of pancreatic necrosis [39].

### Comparison of parenteral and enteral nutrition

**Table 3** gives main results achieved in 6 randomized controlled studies comparing jejunal EN and TPN. No difference was reported concerning mortality rates. However, EN was shown to be associated with a reduction of morbidity [40-44], septic complications [40,41], length of stay in intensive care unit [42], length of stay in hospi-

tal [43,44], and cost of treatment [41,43-45]. These data argue for the use of EN and for the limitation of TPN use in patients 11 with intolerance to EN or in whom EN appears not to be able to satisfy nutritional requirements.

### Indications of nutritional support during acute pancreatitis

Recent consensus publications and reviews made it possible to clarify the indications of nutritional support during acute pancreatitis according the grade of severity [3-7]. Patients with mild or moderate acute pancreatitis are characterized by a spontaneous recovery and do not require EN or TPN. These patients need a few-day fasting associated with etiological treatment, analgesia, fluid and electrolyte replacement. Oral nutrition is usually possible

**TABLE 3.** Randomized studies comparing parenteral and jejunal enteral nutrition in acute pancreatitis (AP). LOS: length of stay; NS: non-significant.

Reference	Patients	Effect on morbidity	Effect on mortality	ICU LOS	Hospital LOS	Effect on costs
[39]	22, emergent surgery	EN reduced morbidity	NS	-	-	EN cheaper than TPN
[44]	30, mostly non severe AP	NS	No death	-	NS	EN cheaper than TPN
[40]	38, severe AP	EN reduced morbidity	NS	NS	NS	EN cheaper than TPN
[41]	14 severe AP, 20 non severe AP	EN reduced morbidity	NS	EN reduced LOS	NS	-
[42]	53	EN reduced morbidity	NS	-	EN reduced LOS	EN cheaper than TPN
[43]	17 severe AP	EN reduced morbidity	NS	-	EN reduced LOS	-

after 3 to 7 day. Diet rich in carbohydrates and moderate in protein and fat has been recommended [7].

Patients with severe pancreatitis, characterized the impossibility of oral feeding for more than 8 days and by a hypercatabolic state, need a nutritional support. The route of nutrient delivery should be determined by patient tolerance [7]. According to present data, EN should be preferred to TPN. TPN should be used in cases with prolonged ileus, when patient do not tolerate EN and when EN is not unable to satisfy nutritional requirements.

According to energy expenditure measurements, energy requirements vary between 25 and 35 kcal/kg/day. It is recommended to avoid over nutrition and to start with 15 to 20 kcal/kg/day in patients with multi-organ failure [7]. Glucose supply should be 3 to 6 g/kg/day, if necessary

associated with insulin in order to maintain blood concentrations < 10 mmol/l. Fat is well tolerated in the absence of hypertriglyceridemia. As in other stress conditions, a fat supply representing 30% of non-protein energy seems has been recommended. The interest of MCT/LCT emulsions, suggested in one study during acute pancreatitis with respiratory distress, needs to be confirmed.

Protein requirements have been estimated at 1.2-1.5 g/kg/day and can reach 1.8 g/kg/day in cases with severe catabolism. More data are needed in order to recommend specific protein supply in these patients.

Vitamin and trace element supplements should be integrated to nutritional support during severe pancreatitis with special attention to vitamins A, C, E zinc and selenium.

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