Nutritional support in acute pancreatitis: from physiopathology to practice. An evidence-based approach

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Abstract. – Acute Pancreatitis (AP) is a potentially fatal syndrome, associated with a hyper-catabolic state as well as early and late complications that may lead to multi-organ failure and death. Clinical researches produced in recent years suggest that acute pancreatitis may benefit from early oral or enteral nutrition. Nevertheless, many clinicians still believe erroneously that fasting – particularly in the early phase – may reduce AP complications and mortality. The goal of our review is to demonstrate that such false belief may harm the patients and that the whole management paradigm must change, adopting a more rational, evidence-based approach. First, we will describe AP physiopathology and the clinical assessment of its severity. Then we will discuss evidence-based data supporting early oral or enteral nutrition in AP. Finally, we will offer some practice recommendations as regards nutritional support.

Key Words:
  Acute pancreatitis, Starvation, Enteral nutrition, Parenteral nutrition.

Introduction

Acute Pancreatitis (AP) is a potentially fatal condition, characterized by:
- Sudden and persistent abdominal pain (often epigastric but also radiating to the back)
- Elevated serum lipase activity (or pancreatic amylase), three times the upper limit of normal range
- Typical findings at abdominal imaging, as obtained by Contrast-Enhanced Computer Tomography (CECT) or – less frequently – by Magnetic Resonance Imaging (MRI) or abdominal Ultrasound (US)[1].

Other clinical features may include fever, leukocytosis, nausea, vomit, and ileus[2].

Etiology of AP may vary, though the most frequent causes are biliary gallstones (40-70%) and alcohol (25-35%). Less common causes are drugs (especially azathioprine and 6 mercaptopurine), primary and secondary hypertriglyceridemia (triglycerides >1,000 mg/dl), congenital anomalies (such as pancreas divisum), infectious diseases (Coxsackie viruses, varicella virus), autoimmunity and genetic disorders[3].

AP incidence varies from 13 to 45 cases per 100,000 worldwide and it seems to be increasing[4,5]. Hospital admissions for AP rose by 20% in the past 10 years, thus increasing health care costs[6].

AP can occur in different patterns, ranging from a mild inflammation to a severe necrosis of the pancreas. In all forms, AP is consistently associated with a systemic inflammatory response syndrome (SIRS) due to a local process of auto-digestion of pancreas and peri-pancreatic tissues.

Mild pancreatitis is often a self-limiting disease leading to no further damage. It occurs in almost 75-80% of cases.

Severe AP, which occurs in the remnant 20-25% of patients, is often characterized by two distinct phases:
- Early phase (within the first week), in which systemic inflammatory response syndrome (SIRS) may progress to multiple organ failures;
- Late phase (after the first week), in which organ failures may become persistent and local complications may arise.

The mortality rate is relatively low (1%) in mild AP, but it can increase to 30% in severe AP. Mortality can be as high as 50% in cases with extensive local necrosis and even to 80% in case of sepsis[7].

The Old Paradigm

Traditionally, nutritional support was not part of AP management, according to the old idea that "to put the pancreas at rest" could be beneficial in the early phases of AP. Furthermore, it was believed also that enteral feeding might have some negative impact on prognosis, by stimulating exocrine pancreatic secretion and, thus, favoring the autolytic processes of the pancreas and the surrounding soft tissues. In this review, we will demonstrate how this old approach is not evidence based and may be detrimental to the patient.

Physiopathology

Metabolic Response to AP

AP is associated with the typical metabolic pattern of a SIRS. AP patients are somehow similar to septic patients in terms of elevated protein catabolism, marked inflammatory state and deranged glucose metabolism (high insulin levels due to a reduced glucose uptake and accelerated neo-glycogenesis)[8,9]. If AP is complicated by sepsis, protein catabolism is further enhanced, up to a net nitrogen loss of 20-40 g/day[8]. Negative nitrogen balance is associated with increased mortality[10].

On the other side, nutrient digestion and absorption may be impaired during an episode of acute pancreatitis, and this may lead to nutritional deficiencies. This would be particularly harmful in patients already undernourished, such as alcoholics, who are at risk of AP. Without nutritional support, patients may rapidly develop severe malnutrition, water retention and decreased muscle function.

Starvation, Gut Bacterial and Inflammatory Mediators Translocation During AP

Increased permeability of the gut mucosa is typical in AP. In an animal model of chemical-induced pancreatitis, Cicalese et al[11] demonstrated that both mild and severe pancreatitis induce bacterial translocation (BT) to the pancreatic gland in 100% of the cases. On the other hand, Kotani et al[12] demonstrated that enteral nutrition (EN) re-duces BT in mesenteric lymph nodes and plasma endotoxin levels in rats with induced AP. Moreover, EN maintains villus height and CD4/CD8 ratio in mesenteric lymph nodes, spleen, and peripheral blood, if compared to PN fed controls. In humans, Xu et al[13] reported a more beneficial effect of EN vs. parenteral nutrition (PN) on gut integrity in 63 patient affected by severe AP. EN was also associated with significantly lower concentrations of plasma endotoxins at any day of observation, compared to PN. In addition, Zhao et al[14] demonstrated a protective effect of EN on the integrity of enteric mucosa in a setting of AP.

Enteral starvation contributes to alter gut mucosa microenvironment, its immune system, and permeability, enhancing the risk of BT.

Hodin et al[15] showed morphological and functional changes in Paneth cells in ileal tissue, after 48 hours of fasting, in a mouse starvation model. These abnormalities were accompanied by a significant BT in mesenteric lymph nodes (twofold increase of colony-forming units per gram of tissue [$p < 0.01$] compared to controls). Heneghan et al[16] recently confirmed these results in parenterally fed mice. Animal experiments carried out by Kang et al[17] showed that total PN results in a rapid and severe atrophy of GALT (gut-associated lymphoid tissue) and increased occurrence of BT. Recently, Ralls et al[18] demonstrated a detrimental effect of starvation on gut EBF (epithelial barrier function) in humans. Analysing tracts of non-inflamed, healthy small bowel obtained from pediatric patients, they assessed trans-epithelial resistance (TER), TNFα and toll-like receptor 4 (TLR-4) in fed and unfed bowels. Fed bowels showed a significantly greater TER than unfed bowels. Immunofluorescence analysis showed a loss of staining intensity for E-cadherin, Claudin-4, and Zonula Occludens-1 (ZO-1) in unfed versus fed bowels; a relative increase in TLRs and TNF-α expression was also found in unfed compared to fed bowels. Previously, the same group had shown similar results in a mouse model[19].

Enteral starvation has also an impact on gut microbiota composition. In PN fed mice there are significant changes in the small intestinal microbiota, resulting in reduced levels of the phylum Firmicutes and increased levels of the phylum Bacteroidetes and Proteobacteria, compared to oral fed mice[20]. As known, Gram-negative bacteria species elicit an inflammatory response via Lipopolysaccharide (LPS) – TLR-4 signalling[21].
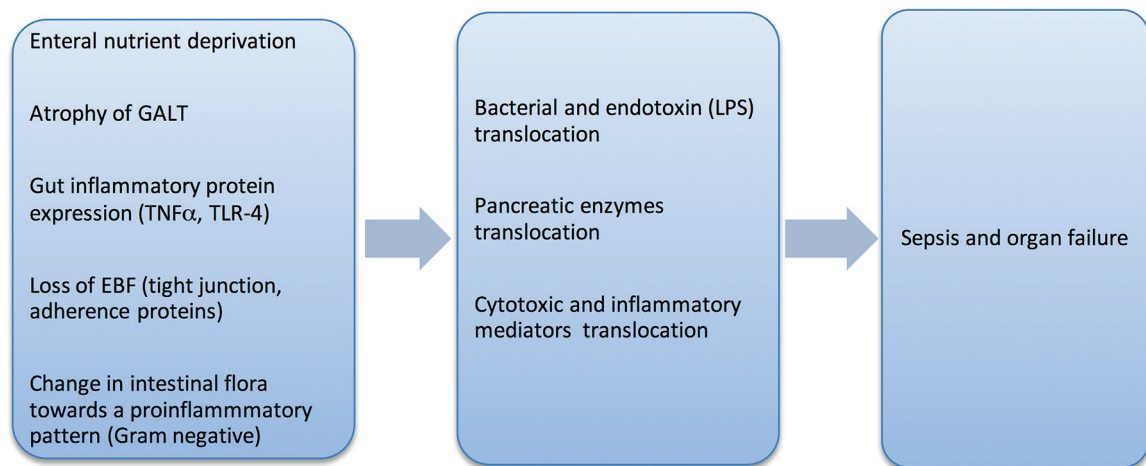
Figure 1. Harmful consequences of PN and enteral starvation. Abbreviations: GALT: Gut Associated Lymphoid Tissue; TNF-α: Tumor Necrosis Factor-α; TLR-4: Toll Like Receptor-4; EBF: Epithelial Barrier Function; LPS: Lipopolysaccharide.

These arguments are even more interesting in the light of the modern theory of "autodigestion" in shock, formulated by Schmid-Schönbein[22,23]. This model proposes a role of pancreatic enzymes in the genesis and pursuance of systemic inflammatory response in shock. The underlying mechanism is supposed to consist in a breakdown of the gut mucosal barrier. In a healthy gut barrier, pancreatic enzymes are exclusively inside the lumen. However, if the mucosal barrier is breached, pancreatic digestive enzymes may escape into the intestinal wall and into the systemic circulation. Inside the intestinal wall such enzymes generate tissue degradation products, among which cytotoxic "unbound free fatty acids" and other inflammatory mediators that flow in the systemic circulation, compromising cell functions and leading to peripheral organ failure.

In summary, prolonged total parenteral feeding may sometimes be mandatory, but it will have negative effects by leading the gut in a state of nutrient deprivation. This condition implies serious side effects, such as atrophy of lymphoid tissue and enhanced permeability of gut mucosa, bacterial translocation and significant changes in intestinal microbiota towards a pro-inflammatory pattern. The loss of gut barrier function also allows the translocation of pancreatic protease and other inflammatory markers involved in organ failure. Clinical consequences are loss of immune reactivity, potential multi-organ failure and increased rate of infectious complications[24,25] (Figure 1).

Assessment of Severity

Severity should be assessed as first as possible on admission, in order to drive the management and to reduce complications[26]. Severity assessment is also important to plan nutrition intervention (see below).

From a radiological point of view, we can classify two types of AP: interstitial edematous pancreatitis and necrotizing pancreatitis. However, these patterns do not completely describe the severity of the disease, but should be integrated with a clinical assessment, considering that radiological findings may vary in the first week after the onset[27] and that the extent of necrosis may be not consistently proportional to the severity of disease[28].

APACHE (Acute Physiologic Assessment and Chronic Health Evaluation) II score is universally recognized as a strong predictive score of severity and mortality in Intensive Care Units, not only in AP but also in several diseases. Released in 1985, APACHE II generates a point score ranging from 0 to 71 based on 12 physiologic variables, age, and underlying health[29]. In AP, at the onset and during the first 72 hours, an APACHE II score < 8 is predictive of low rate of mortality (<4%), while an APACHE II score ≥8 predicts a mortality ranging from 11 and 18%. An APACHE II score increasing in the first 48 hours is strongly predictive of severe acute pancreatitis, while an APACHE II score decreasing in the first 48 hours predicts mild acute pancreatitis[30]. Moreover, in the first 48 hours an APACHE II score >7 is more powerful in predicting severe AP than a Ranson score >

Table I. Modified Marshall scoring system (Atlanta 2012) (modified from Banks PA et al[1]).

Organ System	Score				
	0	1	2	3	4
Respiratory: PaO_2/FiO_2	>400	301-400	201-300	101-200	≤101
Renal: serum creatinine (mg/dl)	< 1.4	1.4- 1.8	1.9- 3.6	3.7- 4.9	>4.9
(μmol/l)	≤134	134- 169	170- 310	311- 439	>439
Cardiovascular: systolic blood pressure (mmHg)	>90	<90 fluid responsive	<90 not fluid responsive	<90, pH < 7.3	<90, pH < 7.2

2 (positive predictive value, negative predictive value, sensitivity and specificity of 55.6%, 97.6%, 83.3%, 91.0% vs. 28.6%, 94.5%, 66.7%, 77.5%)[31]. However, its negative and positive predictive values are limited in the first 24 hours[32].

Levels of serum CRP (C-Reactive Protein) above 150 mg per liter have been considered in several trials as a measure of severe AP[33-35]. At 48 hours after the onset, serum CRP levels > 150 mg/dl have strong sensitivity and specificity, positive and negative value for severe AP[36]. At this time, CRP above this cut-off has also a sensitivity of 80-86% and specificity of 61-84% for diagnosing necrotizing pancreatitis[37]. Khanna et al[38] have demonstrated that, compared with other scores – including APACHE II, Ranson, BISAP (bedside index for severe acute pancreatitis (BISAP) and Procalcitonin (PCT) – CRP had the highest sensitivity (100%), negative predictive value (100%), and specificity (81.4%) for pancreatic necrosis, with a sensitivity of 86.2% and specificity and positive predictive value (PPV) of 100% for prediction of severe AP.

CRP is a simple and inexpensive marker of severe disease in AP. Nevertheless, it cannot be sufficient alone to evaluate patients on the admission, because it is not a disease-specific inflammatory marker and it takes almost 36-72 hours to peak after the onset of symptoms[39].

Obesity, defined as a BMI (Body Mass Index) >30, is a measure of severity and mortality during an attack of acute pancreatitis[40,41]. A meta-analysis by Martinez et al[42] showed a significantly higher rate of severe AP (Odds Ratio [OR] 2.9, 95% Confidence Interval [CI] 1.8-4.6), systemic (OR 2.3, 95% CI 1.4-3.8) and local complications (OR 3.8, 95% CI 2.4-6.6) in obese compared to non-obese patients with AP. A more recent meta-analysis by Chen et al[43] confirmed these data, adding also a significantly higher in-hospital mortality in obese patients affected by AP compared with non-obese ones (Relative Risk [RR] 2.59,

95% CI 1.66-4.03). Given these results, patients with a BMI >30 should be categorized at risk of severe AP.

Atlanta 2012 Classification of acute Pancreatitis[1] put the emphasis on the organ failure. Organ failure has been defined as a score of 2 or more on the modified Marshall score, in at least one of these organ systems: respiratory, renal and cardiovascular (Table I). Organ failure is defined transient if it resolves within 48 hours; permanent if persists for more than 48 hours.

Another characteristic in AP is the presence of complications, local or systemic. Atlanta 2012 classification[1] define as local complications the following findings: acute pancreatic or peri-pancreatic fluid collection, pancreatic pseudocysts, acute necrotic collection and walled off necrosis. These could be sterile or infected. Local complications should be suspected if there is still recurrent abdominal pain, increased serum pancreatic enzymes, organ dysfunction and signs of systemic inflammation (fever, leukocytosis, and inflammatory markers). Generally, local complications appear in the late phase of AP. On the other hand, systemic complications are defined as the exacerbation of pre-existing comorbidities (such as chronic heart or lung diseases).

Given the definitions of organ failure and complications, Atlanta classification establishes different grades of severity in AP:

– Mild acute pancreatitis: characterized by the absence of organ failure and local or systemic complications.
– Moderately severe acute pancreatitis: characterized by transient (<48 hours) organ failure and/or local or systemic complications without persistent organ failure.
– Severe acute pancreatitis: characterized by persistent (>48 hours) organ failure, both single and multiple organ failures.

In the next days of recovery, assessment severity could be done with CT scan according to CT

Table II. Balthazar (CTSI) score (modified from Balthazar[44]).

	Grade	Findings	Score
Pancreatic inflammation	Grade A	Normal pancreas	0 points
	Grade B	Focal or diffuse enlargement of the pancreas	1 point
	Grade C	Abnormality of the pancreas + mild peri-pancreatic inflammatory changes	2 points
	Grade D	Single fluid collection	3 points
	Grade E	Two or more fluid collection or presence of gas in or adjacent to the pancreas	4 points
Pancreatic necrosis		Necrosis absent	0 points
		< 30% necrosis	2 point
		30-50% necrosis	4 points
		> 50% necrosis	6 points

Table III. Assessment of severity during recovery for AP: hours to consider are from the attack of AP.

Assessment	0-24 h	24-48 h	48-72 h
Mild Pancreatitis	APACHE II <8 m. Marshall score <2 No local complications No systemic complications	APACHE II <8 m. Marshall score <2 No local complications No systemic complications CPR ≤ 150 mg/l	APACHE II <8 m. Marshall score <2 No local complications No systemic complications CRP ≤ 150 mg/l Balthazar CTSI 0-3
Moderate Pancreatitis	m. Marshall score >2 and/or Local complications or Systemic complications	m. Marshall score >2 and/or Local complications or Systemic complications	m. Marshall score <2 and/or Local complications or Systemic complications Balthazar CTSI 4-6
Severe Pancreatitis	BMI >30 APACHE II ≥8 m. Marshall score >2	BMI >30 APACHE II ≥8 m. Marshall score >2 CRP > 150 mg/dl	BMI >30 APACHE II ≥ 8 m. Marshall score >2 CRP > 150 mg/dl Balthazar CTSI 7-10

m. = modified; h = hours; APACHE: Acute Physiologic Assessment and Chronic Health Evaluation; BMI: Body Mass Index; CRP: C Reactive Protein; CTSI: CT Severity Index.

severity index (CTSI), released by Balthazar[44]. CT scan gives results that are more reliable if performed 48-72 hours from the onset of an acute attack of AP. CTSI define imaging inflammation in AP stratifying it in five grades (from A to E). For each stage, a point is assigned (from 0 to 4). This number combines with another value based on the presence and extent of necrosis, generating a final score. A sum ranging from 0 to 3 points indicate mild pancreatitis, from 4 to 6 moderate pancreatitis, from 7 to 10 severe pancreatitis (Table II).

In summary, assessment of severity should be performed through multiple systems, integrating clinical, laboratory and radiological findings in several phases of illness (Table III).

Evidence-Based Nutritional Support

Enteral Nutrition Versus Parenteral Nutrition

The effects of enteral and parenteral feeding in pancreatic secretion and metabolism in humans are well known. In healthy subjects, both oral and enteral feeding stimulates amylase, lipase, and trypsin secretion, as well as gastrin and cholecystokinin, whereas PN does not. An elemental enteral formula may reduce enzyme secretion by 50%[45]. On the other side, in acute pancreatitis, both an animal model and a prospective study on patients showed that pancreatic exocrine secretion is suppressed during AP[46,47]. These me-

Table IV. Randomized clinical trials comparing the use of PN and EN in acute pancreatitis.

First Author (Reference)	Year	No. of patients	Setting	Arms	End Points	Results	p-value
Wu XM (50)	2010	107	Severe AP	EN vs. PN	Surgical intervention	22 vs. 80%	<0.05
					Pancreatic septic necrosis	23 vs. 72%	<0.05
					Mortality	11 vs. 43%	<0.05
Doley RP (51)	2009	50	Severe AP	EN vs. PN	Surgical intervention	56 vs. 60%	1
					Infective complications	64 vs. 60%	1
					Hospital stay	42 vs. 36 days	0.755
					Mortality	20% vs. 16%	1
Petrov MS (52)	2006	70	Severe AP	EN vs. PN	Infected pancreatic necrosis	7 vs. 16	0.02
					Multiple organ failure	7 vs. 17	0.02
					Overall mortality	2 vs. 12	<0.01
Targarona Modena J (53)	2006	87	Severe AP	EN vs. PN	Surgical intervention	25% vs. 88%	<0.001
					Infected pancreatic necrosis	20% vs. 74%	<0.001
					Death rate	5% vs. 35%	<0.001
Louie BE (54)	2004	28	Severe AP	EN vs. PN	CRP reduction of 50%	6 vs. 11 days	<0.09
					Dollar ($) per patient	957 $ vs. 2608 $	=0.03
Sun B (55)	2004	100	Severe AP	ISNS vs. PN	Superinfections	8% vs. 30%	<0.05
					Hepatic insufficiency	4% vs. 24%	<0.05
					Intraperitoneal infections	4% vs. 12%	<0.05
					Restoring of oral nutrition	18.5 vs. 24.8 days	<0.05
					Hospital costs in Yuan (¥)	4.1 vs. 5.8 10000 ¥	<0.05
Gupta R (56)	2003	17	Severe AP	EN vs. PN	Hospital stay	7 vs. 10 days	=0.05
					Time to open bowels	1 vs. 2	=0.01
Zhao G (14)	2003	96	Severe AP	EN vs. PN	APACHE II reduction	7.1 vs. 5.7 in 7th day	<0.05
					TNF-α (pg/ml)	43.9 vs. 34.2 in 7th day	<0.05
					CRP (mg/l)	54.3 vs. 41.2 in 7th day	<0.05
					Endotoxin (pg/ml)	5.9 vs. 2.4 in 7th day	<0.05
					L:M ratio in urine	0.097 vs. 0.063	<0.05
Abou-Assi S (57)	2002	53	AP	EN vs. PN	Duration of feeding	6.7 vs. 10.8 days	<0.05
					Median glycemia (mg/dl)	138 vs. 180	<0.03
					Line infections	1 vs. 9	=0.01
					Cost per patient in $	394 $ vs. 2756 $	<0.0004
Windsor AC (58)	1998	34	AP	EN vs. PN	APACHE II in EN group	From 8 to 6 in 7th day	<0.0001
					CRP (mg/l) in EN group	From 156 to 84 in 7th day	<0.005
					(in PN group there were not observed significant changes in 7th day)		
Kalfarentzos F (59)	1997	38	Severe AP	EN vs. PN	Total complications	8 vs. 15	<0.05
					Septic complications	5 vs. 10	<0.01
					Costs of nutrition	30£ vs. 100 £ patient/day	/
Mc Clave SA (60)	1997	30	Mild AP	EN vs. PN	Stress hyperglycemia	Higher in PN	<0.02
					Costs for nutrition in $	761 vs. 3294	<0.001

Abbreviations: AP: Acute Pancreatitis; EN: Enteral Nutrition; PN: Parenteral Nutrition; ISNS: Individually Staged Nutritional Support; CRP: C Reactive Protein; TNFa: Tumor Necrosis Factora; APACHE: Acute Physiology and Chronic Health Evaluation; L:M ratio: Lactulose: Mannitol ratio.

chanisms may explain why EN is safe during an attack of AP[48]. Conversely, PN impairs metabolic response, increasing plasmatic insulin and glucose[49]. These effects of PN may precipitate metabolic response to stress above described, leading to a heavy state of protein catabolism and insulin-resistance. Moreover, PN "puts at rest" the bowels, impairing its absorption and barrier function. We are thus moving toward the antechamber of infection and sepsis.

Randomized Clinical Trials

Many randomized clinical trials (RCTs) have demonstrated the feasibility and better outcomes of EN versus PN in AP. Table IV reports a summary of the published trials on the argument.

Meta-Analyses

Several meta-analyses support the use of EN in AP.

Marik and Zaloga[61] published the first paper, including six RCT (263 patients). They showed a significant lower rate of infections associated with enteral feeding compared with PN ($p=0.004$; relative risk (RR) 0.45; 95%CI: 0.26-0.78). Authors reported also and shorter length of hospital stays in the enteral nutrition group (mean reduction of 2.9 days; $p<0.001$), although there was a significant heterogeneity between studies.

Petrov et al[62], using more homogeneous data, showed in a further meta-analysis a reduced risk of infectious complications ($p<0.001$; RR 0.47; 95% CI: 0.28-0.77), pancreatic infections ($p=0.02$; RR 0.48; 95%CI: 0.26-0.91) and mortality ($p=0.03$; RR 0.32; 95% CI: 0.11-0.98) in EN compared to PN.

Cao et al[63] demonstrated significantly lower risk of infections ($p<0.001$; odds ratio (OR) 0.236; 95% CI: 0.120-0.464), pancreatitis-related complications ($p=0.021$; OR 0.456; 95%CI: 0.234-0.888) organ failure ($p=0.002$; OR 0.334; 95%CI: 0.167-0.670), multiple organ dysfunction syndrome ($p=0.008$; OR 0.306; 95% CI: 0.128-0.736), and mortality ($p=0.005$; OR 0.251; 95% CI: 0.095-0.666). Similar results were also obtained by Yi et al[64] in a further meta-analysis including 8 RCT (381 patients): Authors concluded that total EN is associated with lower mortality, fewer infectious complications, decreased organ failure and surgical intervention rate compared to PN.

Finally, in 2010, a systematic Cochrane review[65] analyzed eight trials (348 patients) comparing EN to PN in AP. Authors found that EN significantly reduces relative risk of death (RR 0.50; 95% CI 0.28 to 0.91), multiple organ failure (MOF) (RR 0.55; 95% CI 0.37 to 0.81), systemic infection (RR 0.39; 95% CI 0.23 to 0.65) and operative interventions (RR 0.44; 95% CI 0.29 to 0.67) compared to PN. Moreover, benefits of EN seem to be more pronounced in patients with severe AP, where the RR of death was lower (RR 0.18; 95% CI 0.06 to 0.58). Authors concluded that EN should be considered the standard of care in patients with AP requiring nutritional support.

Nutritional Routes

All patients affected by AP are at risk of malnutrition, and they should be screened for nutritional support according to international guidelines[66].

There are different times, route and formulas, depending on whether the patient has a mild or severe AP.

Nutrition Support in Mild and Moderate AP

In mild to moderate AP, patients can consume oral food when abdominal pain, nausea, and vomit are reduced, and especially when appetite returns[30,66]. Traditionally, patients are fed in an increasing manner when abdominal pain is absent and pancreatic enzymes are decreasing, starting with clear liquids in the first 24 hours and then assuming a low-fat soft diet, and, if tolerated, after 24 h, a low-fat solid diet[67]. However, a randomized trial comparing oral refeeding with a soft diet with clear liquids in mild AP, revealed no significant difference in clinical outcome in the two groups. Moreover, starting with solid diet is associated with a significantly reduction of the length of hospital stay (median 5 versus 8 days of starting with clear liquids, $p<0.001$)[68]. A more recent, randomized open label trial[69] demonstrated that there was no difference in refeeding tolerance comparing stepwise increasing diet versus immediately full caloric diet.

Fasting due to consistent abdominal pain in mild AP should not exceed five days. In such case, a feeding tube should be placed[30,66,70].

Nutrition Support in Severe AP

All international guidelines[30,66,70-72] state that nutritional support in severe AP should be given by enteral feeding (grade of recommendation: A). EN is to be preferred to PN even if complications such as fistulas, ascites and pseudocysts are present (grade of recommendation: C)[66,70].

EN is feasible and recommended even after surgery for pancreatitis, by intraoperative jejunostomy (grade of recommendation: C)[70]. Enteral tube feeding provides a safe nutritional support in AP even in cases of gastric outlet obstruction[73]. In these case, the tube tip should be placed distal to the obstruction (grade of recommendation: C)[70]. The only actual contraindication to EN is prolonged paralytic ileus. However, even if this case, ESPEN (European Society for Parenteral and Enteral Nutrition) guidelines recommend to combine PN with a small content of an elemental or immuno-enhancing diet (10-30 ml/h) continuously

Table V. Energy requirements in severe acute pancreatitis, according to ESPEN guidelines[72].

Substrate	Quantity	Notes
Proteins	1.2- 1.5 g/kg/day	If not present renal failure or severe hepatic failure
Carbohydrates	3- 6 g/kg/day	Plasma glucose should be $\leq$ 10 mmol/l (180 mg/dl)
Triglycerides	Up to 2 g/kg/day	Plasma triglycerides should be $\leq$ 3 mmol/l (266 mg/dl)

perfused to the jejunum[72]. Regarding the times of supply, continuous infusion is preferred over bolus administration (grade B recommendation)[70].

Energy Requirements

In severe AP, ESPEN guidelines[72] recommend to provide an energy supply of 25-35 kcal/kg/day, with 1.2-1.5 g/kg of protein/day (unless there are renal failure or severe hepatic failure), 3-6 g/kg of carbohydrates/day and up to 2 g/kg of lipid/day. However, plasma glucose concentration should not exceed 10 mmol/l (180 mg/dl) and plasma triglycerides 3-4 mmol/l (266 mg/dl) (Table V).

Nasogastric vs. Nasojejunal Tube

Regarding the placement of the tube, the nasogastric tube has demonstrated to be safe and useful as well as the nasojejunal tube. Two randomized controlled trials[74,75], comparing nasogastric and nasojejunal feeding, concluded that there were no differences in terms of discharge, surgery and mortality rate, between the two ways. A successive meta-analysis[76], involving 157 patients, concluded that there were no significant differences in terms of mortality (RR= 0.69, 95% CI: 0.37 to 1.29, p=0.25), tracheal aspiration (RR= 0.46, 95% CI: 0.14 to 1.53, p=0.20), diarrhea (RR= 1.43, 95% CI: 0.59 to 3.45, p=0.43), exacerbation of pain (RR= 0.94, 95% CI: 0.32 to 2.70, p=0.90) and meeting energy balance (RR= 1.00, 95% CI: 0.92 to 1.09, p=0.97) between nasogastric and nasojejunal feeding. Therefore, a post pyloric placement of the tip is no longer considered necessary (grade of recommendation: B)[30,66,70]. This evidence makes EN more feasible in clinical practice (no more need for endoscopic or radiologic placement of the feeding tube).

Nutritional Formula

Enteral formulas are classified into elemental (monomeric), semi-elemental (oligomeric) and standard (polymeric) formulas[77]. They differ on protein and fat contents.

Elemental formulas contain aminoacids, simple sugars, and very low fats.

Semi-elemental formulas contain peptides of vary chain length, simple sugar, glucose polymers or starch and medium chain triglycerides (MCTs).

Polymeric formulas contain intact proteins, complex carbohydrates and long chain triglycerides (LCTs).

Elemental and semi-elemental formulas have been preferred in many trials on AP, because they have a better profile of absorption than polymeric ones. However, several works have demonstrated that also standard formulations are safe and effective if administered via nasojejunal tube[78-80]. Tiengou et al[81] compared semi-elemental and polymeric formulas in AP in a randomized trial: both were well tolerated, even if, in the semi-elemental group, the length of hospital stay was shorter (23 $\pm$ 2 *vs.* 27 $\pm$ 1, p=0.006). A meta-analysis by Petrov et al[82] about nutrition in AP concluded that the use of polymeric compared with semi-elemental EN formulations did not lead to a significantly higher risk of feeding intolerance, infectious complications or death. Moreover, semi-elemental feeds are sevenfold expensive than polymeric ones[80].

All international guidelines recommend a small peptide and medium chain triglyceride (MCT) oil based formulation (grade B recommendation)[66,70]. ESPEN guidelines[70] recommend peptide-based formulas with a grade A recommendation, even if they acknowledge that a standard formula can be tried if tolerated (grade C recommendation).

The use of glutamine supplementation, immune-nutrition, prebiotics or probiotics is not supported by large-scale studies[83-85]. Conversely, glutamine-supplements are effective in reducing mortality, complications, and length of stay if given in total PN[86], when such approach is inevitable.

Time of Enteral Support

The starting time of enteral support is crucial, because of the issues of gut permeability and BT discussed above. A meta-analysis conducted by Petrov et al[87] and based on 11 RCT (451 patients) found that benefits of EN versus PN, in terms of reduction of MOF, pancreatic infectious complications and mortality rate, were statistically significant if EN was

started within the first 48 hours of admission. After this time, no significant differences were observed in comparison with PN. The advantages of starting EN in AP before 48 hours from the admission have been also observed in more successive studies[88,89] and another meta-analysis[90]. A more recent meta-analysis, conducted on 8 RCT (165 patients) by Bakker et al[91], demonstrated that starting EN within 24 hours after hospital admission, compared with after 24 hours, was associated with lower complications. Among other guidelines, a position paper of the Italian Association for the Study of the Pancreas (AISP)[71] states that EN should be started within 24-48 hours from admission (Evidence level 1, Recommendation grade A).

Conclusions

AP (especially severe AP) is a sepsis-like syndrome characterized by a systemic inflammation (SIRS). Patients affected by AP are consistently at nutritional risk. Intestinal starvation impairs gut barrier and favours BT, leading to sepsis and organ failure.

Severity should be assessed as soon as possible for managing treatment and nutritional route.

Evidence-based data and international guidelines confirm the absolute need of an early oral or enteral feeding, depending on the grade of severity. In mild AP, oral nutrition should be started as soon as the patient reports to be hungry. In severe AP, EN should be started within 24-48 hours from admission. This can be easily ensured in any clinical setting, either via a nasogastric or a nasojejunal tube. Enteral formulas containing small peptides and medium chain triglycerides (MCTs) should be preferred, even though polymeric formulas are equally safe.

In conclusion, a timely and adequate nutritional support may effectively reduce the incidence of infective and non-infective complications, mortality, length of hospital stay and hospital costs associated with AP.

Conflict of Interest

The authors declare no conflicts of interest.

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