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Nutrition Assessment and Therapy in Acute Pancreatitis

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1. Introduction

The impact of nutritional status in acute pancreatitis (AP) has not been fully elucidated, but it is probable that severe malnutrition will adversely affect outcomes, as occurs in other critical diseases. Malnutrition is known to occur in 50-80\% of chronic alcoholics and alcohol is a major etiological factor in AP. Morbid obesity is also associated with poorer prognosis (Gianotti L et al, 2009). Assessment of the severity of AP, together with the patient's nutritional status is crucial in the decision-making process that determines the need or otherwise for nutrition support. Both should be done on admission and at frequent intervals thereafter.

Substrate metabolism in AP is similar to that in response to severe sepsis or trauma. There is an increase in protein catabolism, characterized by an inability of exogenous glucose to inhibit gluconeogenesis, increased energy expenditure, increased insulin resistance and increase dependence of fatty acid oxidation to provide energy substrates. Energy needs may differ and change substantially according to the severity and stage of AP, comorbidities, and specific complications occurring during the clinical course of AP.

Assessment criteria that can serve as early predictors of AP severity are often complex and not sufficiently accurate. However, several recently described criteria that rely on criteria such as the body mass index, physical findings, and simple laboratory measurements could prove useful if validated in large prospective studies (Talukdar R et al, 2009).

The factors that influence mortality in different degrees of severity of AP are various. Etiology, age, sex, race, ethnicity, genetic makeup, severity on admission, and the extent and nature of pancreatic necrosis (sterile vs. infected) influence the mortality. Other factors include treatment modalities such as administration of prophylactic antibiotics, parenteral nutrition (PN) vs. enteral (EN), endoscopic retrograde cholangiopancreatography with sphincterotomy, and surgery in selected cases. Epidemiological studies indicate that the incidence of AP is increasing along with an increase in obesity, a bad prognostic factor. Since Ranson reported early prognostic criteria, a number of attempts have been made to simplify or add new clinical or laboratory studies in the early assessment of severity. Obesity, hemoconcentration on admission, presence of pleural effusion, increased fasting blood sugar, as well as creatinine, elevated C-Reactive Protein in serum, and urinary trypsinogen levels are some of the well-documented factors (Pitchumoni CS et al, 2005).
We found evidence that some indicators of nutritional status could be of help in trying to predict mortality in AP, since nutritional status may be associated with final prognosis. Specifically in the case of severe AP, excess body fat, lack of lean body mass, muscle wasting and poor immune status seems to be related with poor prognosis (Fuchs-Tarlovsky V et al, 2010; Fuchs-Tarlovsky V et al, 1997).

PN in the past has always appeared ideally suited as the preferred route for nutrition support over EN in patients with AP. The pathophysiology of the disease process involves a catabolic stress state, elevated caloric requirements; reduction in pancreatic stimulation or “pancreatic rest” appeared to be needed to allow resolution of inflammation within the gland. However, evidence has emerged that other pathophysiologic processes outside the pancreas itself may contribute to the stress state seen in these patients. Failure to use the gut may actually exacerbate the stress response, prolong the duration and severity of the disease, and increase the likelihood of complications (McClave SA et al, 2006; Lugli AK et al, 2007).

More recent clinical trials have suggested that EN in comparison to PN may maintain gut integrity, reduce intestinal permeability, and down regulate the systemic immune response syndrome (SIRS), thereby favorably affecting clinical outcome (Jabbar A et al, 2003). Further evidence suggests that not only is the route of feeding a factor in outcome, but specific agents in EN or PN (immune-modulating agents) such as probiotics or ω-3 fish oil may influence hospital length of stay (LOS) and rate of complications (Olah A et al, 2002; Laszity N, 2005).

2. Nutrition assessment in AP

Severe AP is associated with high mortality. Adequate nutrition support improves clinical outcome. Nevertheless, several recent trials have focused primarily on the route of nutrition support and neglected the role of nutrition status assessment in tailoring nutrition support to individual needs (Lugli AK et al, 2007).

Definition of an optimal nutritional regimen requires knowledge of energy requirements. Because pancreatitis is a serious disease, it is presumed to be associated with marked increases in energy expenditure. However, data for measured resting energy expenditure (REE) in patients with pancreatitis are limited. In a study aimed to assess the REE of patients with pancreatitis, Dickerson et al found a significantly higher value in those patients complicated by sepsis than those with pancreatitis alone. Septic patients had the largest percentage of hypermetabolic REE, >110% of predicted energy expenditure. They measured REE ranged from 77% to 139% of predicted energy expenditure according to Harris-Benedict equation. The authors concluded that REE is variable in patients with pancreatitis; and the Harris-Benedict equation is an unreliable estimate of caloric expenditure. Septic complications are associated with hypermetabolism and may be the most important factor influencing REE (Dickerson R et al, 1991).

AP increases the catabolism and proteolysis of skeletal muscle by as much as 80% in comparison with normal controls. Further, nitrogen losses have been shown to increase to as much as 20 to 40 g/d (Dickerson R, et al 1991). Decreased levels of total plasma proteins and rapid turnover proteins and marked decrease of the ratio of branched-chain to aromatic amino acid further characterize the hypermetabolic state (Havala T et al 1989; Shaw JHF, 1986). Significant decrease in plasma essential aminoacids, with marked reductions of
almost all amino acids by skeletal muscle mass, have been reported clinically and experimentally (Bouffard YH et al. 1989).

Another study reported the changes in body composition, plasma proteins, and REE during 14 days of PN in patients with AP. Total body protein (TBP), total body water (TBW), and total body fat (TBF) were measured by neutron activation analysis and tritium dilution before and after PN. They studied 15 patients with AP, most of them with severe disease. The gains in body weight, TBW, TBP, Fat Free Mass, TBF and resting energy expenditure after 14 days were not significant. The authors concluded that body composition is preserved in AP during 14 days of PN. In patients without sepsis or recent surgery, PN was able to significantly increase body protein stores (Chandrasegaram MD et al., 2005).

We have found that there are some nutritional parameters associated with mortality in AP. From the nutritional indicators measured, body fat reserves, renal function, muscle mass and immune function were the parameters that associated better with mortality in AP (Fuchs-Tarlovsky et al. 1997). In another study aimed to validate these findings, we found that the group with higher mortality was associated with higher fat reserves, lower immune function or lymphocyte count and lower muscle reserves (Fuchs-Tarlovsky et al., 2010).

3. Pancreatic rest and secretions

Today, the validity of this concept of “pancreatic rest” is no longer accepted (Petrov MS et al, 2008; Ioannidis O et al, 2008; Talukdar R et al, 2009). Efforts to keep up with the increased energy demands in the case of AP are thwarted by the adage to put the pancreas at rest and the avoidance of pancreatic stimulation via gut luminal nutrition. The “pancreatic rest concept” assumes that the pancreatic rest promotes healing, decreases pain, and reduces secretion and leakage of the pancreatic juices in pancreas parenchyma and pancreas tissue (McClave SA et al, 1997). This concept disregards the presence of basal pancreatic exocrine secretion. Protein enzyme output is the responsible component for autodigestion of the gland and perpetuation of inflammatory process. Suppression of protein enzymes output alone with continued bicarbonate and fluid volume output may therefore be adequate in putting the pancreas to rest.

3.1 Pancreatic secretion

Pancreatic secretion and gut motility are tightly interwoven. Basal enzyme secretion is 20% of maximal enzyme secretion and it is regulated by cholinergic and cholecystokinin (CCK)-mediated mechanisms. Feeding by mouth increases pancreatic secretion by involving 3 stimulation levels: cephalic, gastric and intestinal level or phase (Spanier BM et al, 2011). The mere sight of food begins the process of pancreatic secretion and prepares the gut for digestion. Once the food enters the mouth and is chewed and swallowed there is a strong vagal stimulation which fortifies this response. The passage of food into the stomach produces mechanical effects, which further amplify the vagal response and, in addition, lead to gastric acid secretion. Finally, the movement of food and secretions through the pylorus into the duodenum culminates in the maximal stimulatory effect mediated by humoral CCK and secretin and also cholinergic excitation. For many years it was considered that CCK was the chief stimulus for pancreatic enzyme secretion but now it is known that the response is complex and possibly mediated through cholinergic activation (O’Kaffe SJ et al, 2006).
Further studies have demonstrated that as food progresses through the gastrointestinal (GI) tract, there are a series of feedback loops all the way down from the stomach to the colon. Passage of food into the jejunum also inhibits gastric emptying and intestinal transit. The presence of food in the ileum inhibits jejunal motility, presence of nutrients in the ileum inhibits not only pancreatic secretion but also gastric emptying and intestinal transit, and finally the transit of digested food into the colon augments the activation of the ileal brake (Van Citters GW, 1999).

The duration of pancreatic enzyme response increases with greater caloric load. The pancreatic response is also influenced by the physical properties of the meal: mixed solid-liquid meals induce a higher response than liquid or homogenized meals with similar energy content. In both instances, the rate of gastric emptying and thus duodenal delivery of nutrients are the key factors which determine the duration of the pancreatic secretion. The proportion of fat, carbohydrate, and protein contents within a meal also influence the duration and enzyme composition of the pancreatic response (Spanier BM et al, 2011).

3.2 Pancreatic secretion with Enteral Nutrition (EN)

The degree to which the pancreas is stimulated by EN is determined by the site in the GI tract at which feeding is infused. Feeding infused into the jejunum beyond the ligament of Treitz may bypass the cephalic, gastric, and intestinal phase of stimulation of pancreatic secretion, is less likely to stimulate CCK and secretin, and may stimulate inhibiting polypeptides (Abou S et al 2002, Russell MK at al, 2004, Scolapio JS et al, 1999). It has been demonstrated in human studies during jejunal feeding that the pancreatic enzyme output increased significantly over basal levels when it was delivered at the ligament of Treitz, whereas there was no significant increase during more distal jejunal feeding, 60 cm beyond the ligament of Treitz (Vu MK et al, 1999).

Also, the composition of the infused feeds is important. There is some evidence to support an added benefit of elemental formulae for putting the pancreas to rest compared to standard formulae with intact protein or blenderized diets. Elemental diets cause less stimulation than standard formulas, because of their low fat content, the presence of free amino acids instead of intact proteins which bind to free trypsin in the gut, causing trypsin levels to fall, and less acid production from the stomach (Spanier MS et al, 2011).

4. Nutrition therapy

Nutrition therapy in the past has been governed by the principle that the gut should be put at rest with avoidance of any stimulation of pancreatic exocrine secretion. These concepts should now be replaced by the principle that pancreatic stimulation should be reduced to basal rates, but that the gut integrity should be maintained and that the stress response should be contained the likelihood of multiorgan failure (MOF), nosocomial infections, and mortality (McClave SA et al, 1998).

Usually, the initial treatment of AP consists of a nil per os (NPO) regimen and administration of analgesics and ample intravenous fluids (Pandol SJ et al, 2007; Forsmark CE et al, 2007). However, within 24-48 hours EN should be initiated. The rationale for a period without food intake is the assumption that pancreatic stimulation by enteral feeding may aggravate pancreatic inflammation. Moreover, many patients are anorectic and may suffer increasing pain sensation when eating and ileus-related nausea and vomiting, and
delayed return of appetite (Banks PA et al, 2006; Forsmark CE et al, 2007; Meier R et al, 2005; Gianotti L et al, 2009).

There have been studies regarding PN and PN supplemented with special nutrients. A Chinese study by Xian-Li et al evaluated the effects of supplemental parenteral glutamine. Forty one patients with severe AP were randomized to receive either PN or PN with glutamine. Use of PN with parenteral glutamine was associated with significantly less pancreatic infection (0.0% vs 23.8%, p<0.05) and fewer overall complications (20% vs 52%, p<0.05) compared to the use of PN alone without supplemental glutamine (Xian-Li H et al, 2004).

However today’s data trends more to the use of EN rather than PN as will be discussed below.

4.1 Enteral vs Parenteral Nutrition

Traditionally, patients with AP were either treated with strict rest or given PN to allow the pancreas to “rest” until the serum enzyme levels returned to normal. Unfortunately, some disadvantages are associated with the use of PN; one of the most serious is catheter related sepsis. Currently, EN is preferred for patients with AP because it is more cost effective than PN and results in fewer complications (Siow E, 2008).

Despite fears that EN may exacerbate AP because of the stimulatory effect of luminal nutrients on trypsinogen synthesis, several randomized clinical trials have shown that outcome is better and the cost is lower if EN is used instead of PN (McClave SA et al, 1997; Abou-Assi S et al, 2002; Kalfarentzos F et al, 1997). EN can improve survival and reduce the complications accompanying severe AP. The explanations are: EN avoids PN related complications; luminal nutrition maintains intestinal health; enteral aminoacids are more effective in supporting splanchnic protein synthesis; EN may prevent the progression of MOF (Ionnidis O et al, 2008).

In addition to its mucosal protective and immunomodulatory effects, EN is the most effective way of supporting intestinal metabolism. By down-regulating splachnic cytokine production and modulating the acute phase response, EN reduces catabolism and preserves protein (Winsdor AC et al, 1998). In addition, EN with a diet enriched with glutamine has beneficial effect on recovery of IgG and IgM-proteins with a trend to shorter disease duration (Grant J et al, 1984).

There are some clinical studies that compared the use of PN versus EN in AP; the end points analyzed were mortality and complications. From 1996 to 2006 there were 5 studies which studied these outcomes; none of the studies yielded evidence of a difference in the mortality rates between patients given EN and patients given PN. Louie at al reported no deaths among patients given EN and 3 deaths among patients given PN. Those deaths however were attributed to complications of pancreatitis rather than to the mode of nutrition (Louie BE et al, 2005).

Most of the randomized clinical studies reviewed reported higher complication rates among patients given PN than among the EN groups. Kalfarentzos at al reported significantly lower total number of complications for patients given EN compared with the PN group. Complications such as sepsis, nosocomial infection, catheter-related infection, and hyperglycemia are common findings in all studies, especially in patients who were given PN (Kalfarenzos FE et al, 1991). Abou-Assi et al showed a significant difference in rates of catheter-related infections between patients given EN and those with PN. The patients with
infections eventually required removal of the venous catheter and antibiotic treatment (Abou-Assi S et al, 2002). McClave at al. on the other hand, observed equal increases in the risk of infectious complications and the incidences of fluid and electrolyte imbalances (McClave SA et al, 1997).

Louie at al found that the mean number of days of elevated blood glucose levels was 2.7 in the enteral group and 3.6 in the parenteral group (Louie BE, 2005). In all the above mentioned studies, the patients who received EN required fewer days to the start of oral diet than did the PN groups. Abou-Assi et al showed significant evidence that the patients given EN received 4.1 fewer days of nutritional support than the PN group. After disease resolution, 80% of the patients in EN progressed to oral diet without problem, compared with 63% in the PN group (Abou-Assi S et al, 2002).

In addition, all of these clinical trials demonstrated that EN is cheaper than PN. Gupta et al provided significant evidence that patients given EN require a shorter length of hospitalization than patients given PN (Gupta R et al, 2003).

In a recent systematic review about EN vs PN in pancreatitis the authors compared the effect of PN vs EN in patients with AP. The searches or randomized clinical trials were from 2000 to 2008. Eight trials with a total of 348 participants were included. Comparing EN to PN in AP, the relative risk (RR) for deaths was 0.5 (95% CI 0.28 to 0.91), for MOF was 0.55 (95% CI 0.37 to 0.81), for systemic infection was 0.39 (95% CI 0.23 to 0.65), for operative interventions was 0.44 (95% CI 0.29 to 0.67), for local septic complications was 0.74 (95% CI 0.40 to 1.35), and for other local complications was 0.70 (95% CI 0.43 to 1.13). Mean LOS was reduced by 2.37 days in EN vs PN groups (95% CI - 7.18 to 2.44). Furthermore, a subgroup analysis for EN vs PN in patients with severe AP showed a RR for death of 0.18 (95% CI 0.06 to 0.58) and RR for MOF of 0.46 (95% CI 0.16 to 1.29) (Al-Omran M et al, 2010).

McClave et al concluded after performing a systematic review of literature comparing EN vs PN in AP that EN reduces oxidative stress, hastens resolution of the disease process, and costs less. Insufficient data exists to determine whether EN improves outcome over standard therapy. However, in those patients requiring surgery for complications of AP, meta-analysis of 2 trials indicates that provision of EN postoperatively may reduce mortality (RR 0.26; 95% CI 0.0-1.09; p=0.06) compared with standard therapy (McClave SA et al, 2006).

In patients with AP, EN significantly reduced mortality, MOF, systemic infections, and the need for operative interventions compared with those who received PN. In addition, there was a trend towards a reduction in LOS. These data suggest that EN should be considered the standard of care for patients with AP requiring nutritional support. This recommendation is supported by the 2009 American Society for Parenteral and Enteral Nutrition (ASPEN) and Society for Critical Care Medicine (SCCM) Guidelines (McClave SA et al, 2009). Although hypertriglyceridemia may occasionally be the cause of AP, several years of clinical use has shown that PN containing lipid emulsions are safe in this condition (Leibowitz AB, 1992). Serum triglyceride levels should be monitored. Addition of heparin to PN infusate may decrease triglyceride levels in some patients (Benderly A et al, 1983). Table 1 summarizes the available information on the special nutrients in enteral feedings.

4.2 Nasojejunal (NJ) vs Nasogastric feeding (NG)

NJ feeding tubes are placed blindly at the bedside, expecting spontaneous transpyloric migration or by using endoscopic or radiologic control.
<table>
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<tr>
<th>Reference Author, year</th>
<th>Study design</th>
<th>Type of nutrition</th>
<th>Results</th>
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<tbody>
<tr>
<td>Abou –Assi et al, 2002</td>
<td>Randomized controlled</td>
<td>EN(NJ) vs. PN</td>
<td>Duration of feeding was shorter in the EN (6.7 vs. 10.8 days, p&lt;0.05) and nutrition costs were lower in the EN group. Metabolic (p&lt;0.003) and septic (p=0.01) complications were lower in the EN group.</td>
<td>EN seems to be safer and less expensive than PN in AP.</td>
</tr>
<tr>
<td>Kalfarentzos F et al, 1997</td>
<td>comparative clinical trial</td>
<td>EN vs. PN</td>
<td>Patients who received EN experienced fewer complications (P&lt;0.05), specially septic complications (P&lt;0.01) than those receiving PN. PN costs were three times higher than EN.</td>
<td>EN should be used preferentially in patients with severe AP.</td>
</tr>
<tr>
<td>Winsdor AC et al, 1998</td>
<td>Randomized controlled</td>
<td>EN vs. PN</td>
<td>The acute phase response and disease severity scores were significantly improved following EN (CRP: 156(117-222) to 84(50-141), p&lt;0.005; APACHE II scores 8(6-10) to 6(4-8), P&lt;0.0001) without change in the CT scan scores. In the PN group, these parameters did not change but there was an increment in the EndoCAb antibody levels and reduction in the CT scan scores. EN did not show changes in the level EndoCAb level but there was an increase in the CT scan scores.</td>
<td>EN moderates the acute phase response, and improves disease severity and clinical outcome despite unchanged pancreatic injury on CT scan. EN reduced systemic exposure to endotoxin and reduced oxidative stress; it also modulates the inflammatory and sepsis response in PA.</td>
</tr>
<tr>
<td>Luie BE et al, 2005</td>
<td>Randomized controlled</td>
<td>PN vs. EN</td>
<td>Reduction of CRP levels by 50% was 5 days faster with EN than with PN. Nutrition support costs were lower in the EN group.</td>
<td>EN shows a trend toward faster attenuation of inflammation, with fewer septic complications and is the preferred therapy in terms of cost – effectiveness.</td>
</tr>
<tr>
<td>Gupta R et al, 2003</td>
<td>Randomized controlled</td>
<td>EN vs. PN</td>
<td>Fatigue improved in groups but faster with EN. Oxidative stress was similar in both groups. There were no significant differences in complication rate and LOS was shorter in EN group (7(4-14) vs 10(7-26) days; p=0.05) The cost in the EN group was considerably less than PN.</td>
<td>EN is safe in severe AP. It is as effective as PN and may be beneficial in the clinical course of disease.</td>
</tr>
</tbody>
</table>

Abbreviations: AP= Acute Pancreatitis / EN = Enteral Nutrition / PN = Parenteral Nutrition / LOS = Length of Hospital Stay

Table 1. Comparative studies between EN and PN
Eatock at al. performed a randomized controlled study on early NG versus NJ feeding in severe AP (Eatock FC et al., 2000; Eatock FC et al., 2005). They found that NG feedings were very well tolerated and recommended that NG feedings should be considered a therapeutic option because of its simplicity, obviating the need for endoscopic or radiologic procedures. This study had several limitations, one of them being the failure to fluoroscopically confirm that the NJ tubes were appropriately positioned in the jejunum. There is no indication whether the NJ tubes were placed distal enough (at least 60 cms from the ligament of Treitz) to avoid gastric and pancreatic stimulation. The failure to find difference may have been related to continued gastric and duodenal stimulation occurring in both groups of patients. Similar findings from randomized studies were reported by Eckerwall et al who performed a randomized clinical trial to compare the efficacy and safety of early EN via NG tubes with PN. The authors reported that early NG EN in patients with severe AP was feasible, and resulted in better glucose control. No beneficial effects on the intestinal permeability or on the inflammatory response were seen by EN treatment (Eckerwall GE et al, 2006).

Kumar et al performed a randomized clinical trial to compare early NJ with NG feeding in severe AP, and showed that that EN at a slow infusion is well tolerated by both NJ and NG routes in patients with severe AP. Neither feedings leads to recurrence or worsening of pain in patients with severe AP. They also reported that nutritional parameters remained unaffected because of inadequate caloric intake during the first week of feeding (Kumar A et al, 2006).

Vu et al studied the activation of pancreatic secretion in 8 healthy volunteers in response to proximal or more distal jejunal delivery of nutrients into the small intestine. The authors concluded that continuous feeding into the distal jejunum does not stimulate exocrine pancreatic secretion (Vu MK et al, 1999).

Piciucchi M et al assessed the rate of spontaneous tube migration and to compare the effects of naso-intestinal (NI) tube feeding in AP. They defined NI location as those tubes placed beyond the ligament of Treitz. The authors showed that spontaneous tube migration to an NI site occurred in 10 of 25 or 25% of the patients, while in 15 (60%) EN was started with an NG tube. EN through NG or NI were similar in terms of tolerability, safety, clinical goals, complications and hospital stay. As a conclusion, EN by NG tubes seem to provide a pragmatic alternative opportunity with similar outcomes in AP (Piciucchi M et al, 2010).

McClave SA et al also commented in their meta-analysis that a wide range of tolerance to EN exists, irrespective of known influences such as mode (continuous versus bolus) and level of infusion within the GI tract (gastric versus postpyloric) (McClave SA et al, 2006). Patients with severe necrotizing pancreatitis may have gastric outlet obstruction or severe gastroparesis and many may have to be approached differently. Feeding into the stomach may be ineffective and possibly hazardous. Further multicenter randomized trials studies are needed to confirm whether NG feeding is a practical and effective form of management for patients with severe AP (Ioannidis O et al, 2008). Table 2 summarizes the available information on the special nutrients in enteral feedings.

### 4.3 When to start nutrition support

Per oral ingestion of nutrients is often hampered by abdominal pain with food aversion, nausea, vomiting, gastric atony, and paralytic ileus or by partial duodenal obstruction from pancreatic gland enlargement. The application of early EN may be limited by the severity of the pancreatitis attack and the occurrence of ileus (Spanier BWM, et al. 2011).
<table>
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<tr>
<th>Reference</th>
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<tr>
<td>Eatock FC et al, 2005</td>
<td>Randomized controlled comparative clinical trial</td>
<td>NG vs. NJ</td>
<td>Clinical differences between the two groups were not significant. Overall mortality was 24.5% with five deaths in the NG group and seven in the NJ group.</td>
<td>The simpler, cheaper, and easier to use NG feeding is as good as NJ feeding in patients with objectively graded severe AP.</td>
</tr>
<tr>
<td>Kumar A et al, 2006</td>
<td>Randomized controlled comparative clinical trial</td>
<td>NJ vs. NG</td>
<td>Group 1 (NG): Diarrhea occurred in 4 patients and there were 5 deaths, 1 patient underwent surgery. Group 2 (NJ): Diarrhea occurred in 3 patients, there were 4 deaths, and 2 patients underwent surgery.</td>
<td>EN at a slow infusion is well tolerated by both NJ and NG routes in patients with AP. Neither NJ nor NG feeding leads to recurrence or worsening of pain in AP. Nutritional parameters remained unaffected because of inadequate calorie intake during the first week of feeding.</td>
</tr>
<tr>
<td>Piciucchi M et al, 2010</td>
<td>Randomized controlled comparative clinical trial</td>
<td>NG vs. NJ</td>
<td>Spontaneous tube migration to NJ site occurred in 10/25 (40%) prospectively enrolled severe AP patients; while in 15 (60%) nutrition was started with a NG tube. CT severity index was higher in NG tube patients than in NI (mean 6.2 vs. 4.7, P = 0.04).</td>
<td>Spontaneous distal tube migration is successful in 40% of severe AP patients, with higher CT severity index predicting IG retention; in such cases EN by NG tubes seems to provide a pragmatic alternative opportunity with similar outcomes.</td>
</tr>
</tbody>
</table>

Abbreviations: AP= Acute Pancreatitis / NJ = Nasojejunal feeding / NG = Nasogastric feeding / IG = Intragastric/NI=Nasointestinal

Table 2. Comparative studies between NJ and NG

The precise timing for initiating enteral support has not been specifically addressed in the pancreatitis population but has been studied to a large extent in the critically ill population. EN has been described as a rational and acceptable option of supporting critically ill patients after major abdominal surgery, as well as in patients with AP (Windsor AC et al, 1998). Early EN starting prior to 48 hours from admission in critically ill patients is associated with a significant 24% reduction in infectious complications and 32% reduction in mortality.
compared with delay feedings started after that point time (McClave SA et al, 2009; Heyland DK et al, 2003).

Oláh et al demonstrated that early jejunal feeding with an elemental diet within 48 hours after the onset of symptoms when possible, and was more useful and cheaper than PN. They concluded that early jejunal feeding reduced septic complications in necrotizing AP in combination with adequate antibiotic prophylaxis (Oláh A et al, 2002).

Pupelis G et al performed a randomized clinical trial measuring the feasibility and effectiveness of jejunal feeding after surgery due to peritonitis in severe AP. They concluded that early jejunal feeding resulted in 3.3% mortality as opposed to 23.3% in the control group (p=0.05) and that jejunal feeding is feasible and effective in postoperative treatment of patients due to secondary peritonitis because of AP (Pupelis G et al, 2001). Table 3 summarizes the available information on the special nutrients in enteral feedings.

<table>
<thead>
<tr>
<th>Author, reference, year</th>
<th>Study design</th>
<th>Time to start nutrition therapy</th>
<th>Results</th>
<th>Conclusion</th>
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<tbody>
<tr>
<td>Pupelis G et al, 2001</td>
<td>Randomized controlled comparative clinical trial</td>
<td>Patients in EN group received the daily mean of 1294.6 (362.6) kcal including 830.6 (372.7) kcal enterally, versus 472.8 (155.8) kcal daily in the control group (P &lt; 0.0001).</td>
<td>The first surgical intervention resulted in 3.3% of re-laparotomies in EN patients, caused by unresolved peritonitis, versus 26.7% in the control subjects (P = 0.03). Recovery of bowel transit took significantly less time in the EN patients (mean: 54.6 h versus 76.8 h in control subjects, P = 0.01). EN resulted in 3.3% mortality as opposed to 23.3% in the control group (P = 0.05).</td>
<td>EN is feasible and effective in postoperative treatment of patients due to secondary peritonitis or severe pancreatitis. Improved bowel and peritoneal function could be the main impact of EN.</td>
</tr>
<tr>
<td>Oláh et al, 2002</td>
<td>Randomized controlled comparative clinical trial</td>
<td>1st phase: PN was compared with early (within 24-72 h after the onset symptoms) EN.</td>
<td>Septic complications were lower in the EN group (P = 0.08, chi(2) test)</td>
<td>The combination of early EN and selective, adequate antibiotic prophylaxis may prevent multiple organ failure in patients with AP.</td>
</tr>
<tr>
<td>Kalfarentzos, 1991</td>
<td>Randomized controlled comparative clinical trial</td>
<td>Group 1: EN in the first 72 hours an EN later in the course of the disease</td>
<td>Group 1: 23% complications and 13% mortality Group 2: 95.6% complications rate and 38% mortality P&lt;0.01</td>
<td>Early EN reduced complications rate and mortality in AP</td>
</tr>
</tbody>
</table>

Abbreviations: Se=Selenium / AP= Acute Pancreatitis / EN = Enteral Nutrition

Table 3. Comparative studies between early and late EN
4.4 Types of enteral formula recommended

A few studies to date compare the results of feeding elemental, semielemental, and polymeric diets to patients with AP (Marik PE, 2009 and Talukdar R et al, 2009). Elemental formulas are completely predigested and consist of aminoacids, simple sugars, and enough fat to prevent essential fatty acid deficiency. Semielemental formulas required less digestion than polymeric foods and contain peptides of varying chain length, simple sugars, glucose polymer, or starch and fat primarily as medium chain triglycerides. Polymeric feeds contain non-hydrolyzed proteins, complex carbohydrates, and longchain triglycerides. Based on the assumption that elemental and semielemental formulas cause less pancreatic stimulation than standard formulas, most EN studies have used an elemental or semielemental formula. Although there is a variety of data on the use of standard enteral formula in such patients (Spanier BWM et al, 2011), both Windsor et al and Pupelis et al have shown that polymeric formula can be safely fed through jejunal tubes in AP patients (Windsor ACJ, 1998; Pupelis G et al., 2001).

A few studies have defined the benefits of semielemental versus polymeric formulas in severe AP. Cravo et al found a similar tolerance in 102 patients with AP given semielemental versus polymeric formulas (Cravo M et al, 1989). In a randomized trial using semielemental and polymeric formulas in 30 AP patients, Tiegou et al showed that both formulas were well tolerated and well absorbed, but the semielemental group had less weight loss and shorter LOS compared with the polymeric group (Tiegou IE, 2006). Petrov et al performed an adjusted meta-analysis using 20 randomized controlled trials, including 1070 patients. None of the studies was associated with a significant difference in feeding tolerance when comparing the tolerance and safety of EN formulations in patients with AP. The use of a semielemental diet versus polymeric formulation did not show significant differences (RR= 0.62). The authors concluded that the use of polymeric compared with semielemental formulation, does not lead to a significant higher risk of feeding intolerance, infectious complications, or death in AP patients (Petrov MS et al, 2008; Petrov MS et al, 2009). Table 4 summarizes the available information on the special nutrients in enteral feedings.

It should be remembered that semielemental or elemental diets are sevenfold as expensive as polymeric feeds, and in some countries perhaps even more expensive. In summary, the evidence base to use just semielemental or elemental formulas becomes less clear (Spanier BWM et al, 2011).

4.5 Use of supplements or special nutrients in Enteral Nutrition

The routine use of glutamine, immunonutrition, prebiotics and probiotics in AP is not supported by large scale clinical studies. Two studies evaluated immune-enhancing formulas that contain glutamine, arginine and fibers or glutamine, arginine and ω-3 fatty acids, vitamins, and micronutrients (Hallay J et al, 2001; Pearce CB et al, 2006). Hallay et al compared a standard formula with a glutamine-enriched formula on immunologic parameters in 16 patients with AP; they found that the recovery of the immunological parameters was better and the time of disease recovery was shorter in the glutamine treated group. Other authors also reported the beneficial effect of a glutamine-rich multifiber diet as compared to a standard fiber diet; the trend of IgG and IgM, as well as visceral proteins (prealbumin and Retinol Binding Protein) with shorter disease duration was seen in the treatment group (Hallay J et al, 2001).
### Table 4. Comparative studies between the efficacies of the different types of EN

<table>
<thead>
<tr>
<th>Author, reference, year</th>
<th>Study design</th>
<th>Types of formula</th>
<th>Results</th>
<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>Tiegou IE, 2006</td>
<td>Randomized comparative prospective controlled clinical trial</td>
<td>Semi-elemental vs polymeric formula.</td>
<td>Tolerance was good in both groups (semi-elemental vs. polymeric: VAS, 7.4 +/- 0.6 vs. 7.1 +/- 0.6 NS; number of stools per 24 hours, 1.7 +/- 0.4 vs. 1.8 +/- 0.4, NS). Steatorrhea was lower than normal in both groups. In the semi-elemental formula group, the hospital LOS was shorter (23 +/- 2 vs. 27 +/- 1, p = .006) and weight loss was less marked (1 +/- 1 vs. 2 +/- 0, p = .01). One patient in semi-elemental group and 3 patients in polymeric group developed an infection (NS).</td>
<td>Semi-elemental and polymeric nutrition are very well tolerated in patients with AP. Nutrition with a semi-elemental formula supports the hypothesis of a more favorable clinical course than nutrition with a polymeric formula.</td>
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<tr>
<td>Windsor ACJ, 1998</td>
<td>Randomized Clinical trial</td>
<td>Polymeric formula “Osmolite”®, “Fresubin”®</td>
<td>Following seven days of enteral nutritional support there was a significant reduction in serum CRP from 156 (117–222) mg/l to 84 (50–141) mg/l (p&lt;0.005) and APACHE II scores fell from 8 (6–10) to 6 (4–8) (p&lt;0.0001) in the enterally fed group.</td>
<td>Polymeric formula can be safely fed through NJ tubes in AP patients. Enteral feeding in acute pancreatitis is practical. Furthermore is both feasible and desirable in the management of patients with acute pancreatitis.</td>
</tr>
<tr>
<td>Cravo M et al, 1989</td>
<td>Prospective</td>
<td>Elemental (group 1/ n=47) vs polymeric formula (group 2 / n=44)</td>
<td>Mean nutrient intake was higher in group II (p&lt;0.001): Kcal: 1447±228 vs 1161±182; protein: 45±9 vs 30±8g; fat: 31±10 vs 4±3g. Local complications rate was similar (17% in group I vs 7% in group II) and LOS was: In group I 6.6±3.2 vs Group II 6.3±2.2d.</td>
<td>Elemental diets offer no advantage upon polymeric balanced diets.</td>
</tr>
</tbody>
</table>

Abbreviations: NS=Non significant / AP= Acute Pancreatitis / EN=Enteral Nutrition /NJ=Nasojejunal/ LOS=Length of hospital stay
Pearce et al supplemented arginine, glutamine, ω-3 fatty acids and antioxidants in 31 patients with severe AP in a randomized control trial; their findings suggest that an increase in C-Reactive Protein was found in the supplemented group compared with the control group. No significant differences were found in the length of hospital stay. Although a lower incidence of pneumonia and MOF, and shorter length of ICU and hospital stay was observed in the immunonutrition group, none of these differences reached statistical significance (Pearce CB et al, 2006).

De Beaux et al randomized 14 patients with severe AP to receive standard PN of isocaloric, isonitrogenous, glutamine-enriched PN; only 13 patients completed the study. There was a trend for the glutamine supplemented group to show improved lymphocyte proliferation, increased T-cell DNA synthesis and decrease release of the pro-inflammatory cytokine IL-8 (De Beaux AC et al, 1998).

A double blind randomized clinical trial by Olah et al evaluated the effects of probiotics added to EN. They proposed that the rapid disappearance of commensal flora in AP, combined with overgrowth of potentially pathogenic organisms, provided the rationale for probiotic therapy. The authors divided patients into 2 groups; the treatment group, who received a preparation containing Lactobacillus plantarum together with a substrate of oat fiber for one week by NJ tube; and the control group who received heat inactivated Lactobacillus strain preparation. Infected pancreatic necrosis and abscesses occurred in 4% of the patients in the treatment group as compared to 30% in the control group (p=0.023). The mean hospital LOS was shorter in the treatment group as well (p<0.05) (Olah A et al, 2002).

Lasztity evaluated whether provision of ω-3 polyunsaturated fatty acids (ω-3 PUFA) or fish oil could alter the course of disease in AP through modulation of eicosanoid synthesis. Supplementation of EN with 3.3 g/d of ω-3 PUFA for 7 days in the treatment group resulted in a significant decrease in hospital LOS (p<0.05) and duration of nutrition therapy (Lasztity N, 2005).

<table>
<thead>
<tr>
<th>Author, reference, year</th>
<th>Study design</th>
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<th>Results</th>
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<tr>
<td>Hallay J et al, 2001</td>
<td>Randomized clinical trial</td>
<td>“Stresson” ® Multi Fibre vs “Nutrison” ® Fibre</td>
<td>The treatment with glutamine-rich “Stresson” ® resulted in significant elevations in the serum levels of IgG, retinol binding protein, compared to the effects of Nutrison Fibre. In addition, the recovery of treated patients was significantly shorter in the “Stresson” ® Multi Fibre group than in the “Nutrison” ® Fibre group.</td>
<td>The “Stresson” ® Multi Fibre nutrient treatment of patients treated for AP seems to have clinical benefit based upon the fast recovery of IgG, IgM proteins and the immunological defense mechanisms.</td>
</tr>
<tr>
<td>Pearce CB et al, 2006</td>
<td>Double-blind Randomized controlled trial</td>
<td>Glutamine, arginine, tributyrin and antioxidants vs an isocaloric isonitrogenous</td>
<td>After 3 days of feeding, in the study group 2/15 (13%) of patients had reduced their CRP by 40 mg/L or more. In the control group 6/16 (38%) of patients had reduced their CRP by this</td>
<td>The cause of the unexpectedly higher CRP values in the study group is unclear.</td>
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<tr>
<td>Author, reference, year</td>
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<td>Results</td>
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<td>Oláh A et al, 2002</td>
<td>Randomized clinical trial</td>
<td>Group 1: Received Lactobacillus plantarum together with a substrate of oat fibre. Group 2 (control): Received a isonitrogenous formula but the Lactobacillus was inactivated by heat.</td>
<td>Infected pancreatic necrosis and abscesses occurred in 1 of 22 patients in the treatment group, compared with 7 of 23 in the control group (P = 0.023). The mean length of stay was 13.7 days in the treatment group versus 21.4 days in the control group (p=NS).</td>
<td>Supplementary L. plantarum was effective in reducing pancreatic sepsis and the number of surgical interventions.</td>
</tr>
<tr>
<td>Lasztity, 2005</td>
<td>Randomized clinical trial</td>
<td>N-3 PUFAs (fish oil) enterally (3.3g/day for 5-7 days).</td>
<td>The n-3 to n-6 LCPUFA ratios increased significantly in serum lipids of the patients receiving supplementation. The SOD activity was significantly higher at day 3 in the supplemented group (P&lt;0.05).</td>
<td>The use of enteral formula enriched with n-3 PUFAs in the treatment of AP seems to have clinical benefits based upon the shortened time of jejunal feeding and hospital stay.</td>
</tr>
<tr>
<td>Kuklinski B et al, 1995</td>
<td>Randomized clinical trial</td>
<td>Antioxidant treatment sodium selenite as a water soluble redox substance represented an alternative</td>
<td>With a well-timed selenium therapy the rates of lethality complications and operation dropped drastically. Complications occurred if the therapy began too late (if patients were administered too late) and in biliary forms.</td>
<td>An improvement in the prognosis of acute pancreatitis can be achieved if antioxidant selenium therapy with sodium Se is introduced in time. In rare cases total necroses and complications in organs only occurred in those patients who were admitted to this therapy too late.</td>
</tr>
</tbody>
</table>

Abbreviations: Se=Selenium / AP= Acute Pancreatitis / PUFA = Polyunsaturated fatty acids / SOD= Superoxide dismutase

Table 5. Special Nutrients in Enteral Feeding

In a study by Kuklinski et al. reduction of plasma selenium levels was noted in patients with AP; positive results after the addition of selenium into the intestinal diet of these patients
was reported (Kuklinski B et al, 1995). Despite the limited number of reports on this subject, the European Society of Parenteral and Enteral Nutrition (ESPEN) Guidelines recommend the use of PN with selenium in patients with AP (Meier R et al, 2006).

In summary, the beneficial effect of EN on patient outcome in AP may be enhanced by providing certain supplements. Although adding arginine, glutamine, ω-3 fatty acids, or specific probiotic preparation to the EN in patients with AP may result in reduction of hospital LOS, duration of nutrition therapy, or certain complications (when compared with the use of EN alone without the supplements), not enough information is available to make firm and specific recommendations. The addition of parenteral glutamine to PN should be considered in order to shorten hospital LOS and duration of nutrition therapy (when compared with PN alone without the supplement (McClave SA et al, 2006). Table 5 summarizes the available information on the special nutrients in enteral feedings.

5. Conclusions

Most patients with AP have mild disease and do not need additional nutrition support during admission. According to guidelines, nutritional support is generally indicated if patients cannot consume normal food after 5-7 days when it becomes evident that the patients will not be able to tolerate oral intake for prolonged period of time (7 days or more) (Spanier BM et al, 2011). However, in a malnourished patient, especially if critically ill, nutrition therapy in some form must be provided earlier, to avoid caloric deficits. Nutrition therapy by enteral route is now the modality of choice for patients with severe AP. Recent guidelines have summarized the levels 1 and 2 evidence in support of the preferred role of EN according to safety, cost, and ease of administration. Patients with AP should be provided EN early because such therapy modulates the stress response, promotes more rapid resolution of the disease process, and results in better outcome. EN has beneficial influence on the disease course and should be initiated as early as possible (within 48 hours of admission). Large multicenter studies are still needed to confirm the safety and effectiveness of NG feeding when compared with NJ feeding and to investigate the role of early (within 48 hours) versus late nutrition support. When distal jejunal access is not possible to attain or maintain, intragastric feeding can be cautiously initiated, following safe practice standards. The clinical evidence to use semi elemental diets is still weak. Routine use of supplementation formulas with glutamine and probiotics or immune-enhancing diets in AP cannot be recommended at this time.

6. References


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Acute Pancreatitis (AP) in approximately 80% of cases, occurs as a secondary complication related to gallstone disease and alcohol misuse. However there are several other different causes that produce it such as metabolism, genetics, autoimmunity, post-ERCP, and trauma for example... This disease is commonly associated with the sudden onset of upper abdominal pain that is usually severe enough to warrant the patient seeking urgent medical attention. Overall, 10-25% of AP episodes are classified as severe. This leads to an associated mortality rate of 7-30% that has not changed in recent years. Treatment is conservative and generally performed by experienced teams often in ICUs. Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, the presence of complications has a significant prognostic importance. Necrosis, hemorrhage, and infection convey up to 25%, 50%, and 80% mortality, respectively. Other complications such as pseudocyst formation, pseudo-aneurysm formation, or venous thrombosis, increase morbidity and mortality to a lesser degree. The presence of pancreatic infection must be avoided.

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