THE ROLE OF NUTRITIONAL SUPPORT IN ACUTE PANCREATITIS: A REVIEW AND PROPOSAL OF A CLINICAL PATHWAY FOR MANAGEMENT

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ABSTRACT: The aim of this review is to critically analyse the available literature and to propose a rational, safe and cost-effective clinical pathway to provide nutritional support in acute pancreatitis. This pathway is proposed based on assessment of peer reviewed literature and existing generally accepted knowledge.

Acute pancreatitis is a heterogeneous disease and the outcome is variable. The role of nutritional support is controversial. Acute mild pancreatitis (80%) usually does not require nutritional support unless the pre-existing nutritional is poor or complications occur. Contrary to this acute severe pancreatitis is associated with severe catabolism and a high complication rate. Nutritional depletion rapidly occurs. It is logical to support the nutrition once the patient is haemodynamically stable. Although enteral nutrition should be administered whenever feasible, it is not always possible or advisable. Aggressive, hypercaloric parenteral nutrition administered via central venous line is not recommended. A combination of initial peripheral parenteral nutrition with fat in appropriate amount, and gradually switching over to enteral feedings is safer and cost-effective. It also avoids central line associated sepsis. The roles of newer specific therapeutic diets to enhance the immune status in patients with acute pancreatitis are not well established. *(JUMMEC 1999; 2: 81-87)*

KEYWORDS: Acute pancreatitis, Enteral nutrition, Parenteral nutrition, Immunonutrition.

Introduction

Acute pancreatitis is a disease that results in autoactivation of pancreatic enzymes, leading to inflammation and autodigestion of the gland, and peripancreatic tissues. It is common in adults and uncommon in children. In adults biliary tract disease, alcoholism and trauma are the common causes (1). In children the causes are more diverse. Congenital anomalies, trauma, viral infections, drugs, and worm infestation are the leading causes (2). The resulting inflammation varies from mild oedema of the pancreas to severe pancreatic necrosis and abscess formation, and may later result in loss of endocrine and exocrine function. In 80% of the cases, the disease is mild and usually resolves)ân a week (3). The presence of organ failure or evidence of pancreatic necrosis on dynamic CT scan differentiates severe pancreatitis (20% of the cases) from mild cases. They have a more protracted course and higher mortality and are more likely to require nutritional support. In 25% of these patients pseudocysts, intestinal and pancreatic fistulas, pancreatic abscesses and pancreatic ascites can occur (1,4,5,6,7).

Metabolic response to pancreatitis

Severe pancreatic inflammation leads to metabolic abnormalities similar to sepsis. Energy expenditure is increased further when infectious complications occur (4, 5, 8). Indirect calorimetric studies have shown an increase in Resting Energy Expenditure. A hypermetabolic state occurs in about 65% of them. In 35% there may be normometabolism and in 10% there may be hypometabolism (3,9,10).

During the hypermetabolic state the energy expenditure and oxygen demand are increased. There is increase in gluconeogenesis. In addition peripheral and hepatic insulin resistance occurs and results in hyperglycaemia. Cataboiism and protein breakdown especially from skeletal muscle raises the concentrations of aromatic amino acids, decreases levels of branched

chain amino acids, and accelerates ureagenesis (3, 9, 11). Skeletal muscle glutamine level reduces considerably to as low as 15%, and serum glutamine levels may drop to as low as 55% of normal (3,4). Hypocalcaemia and hypomagnesaemia may occur. Ten to 15% may develop hypertriglyceridaemia (1,4). Most hypertriglyceridaemia seen in association with pancreatitis are related to metabolic abnormalities secondary to illness, rather than as a primary causative factor (12).

Why nutritional support ?

The net result in acute severe pancreatitis is marked catabolism, and if not supported leads to, or, aggravates pre-existing malnutrition (4,7,13). In Feller's series 42% of 200 patients developed severe malnutrition and it was regarded as a complication of acute pancreatitis (14). Nutritional depletion may increase the risk of, or may modify the response, to infection and may lead to increased morbidity and mortality.

Review of the literature suggests that there is no level I evidence that nutritional support is beneficial in acute pancreatitis (3,5,12,15,16). Most of the studies are in acute severe pancreatitis, there are few studies comparing TEN with TPN (5, 18,19,20). It is difficult to draw definitive conclusions from these studies because each one uses different criteria to indicate severity (Ranson's or Imrie or Glasgow), and different levels of score in the APACHE II system, varying from >7 to >9 to indicate severity. The study population is also not adequate in each group. It is difficult to demonstrate that a difference is truly present when the study population is small (Type II error). In addition there are no prospective randomized controlled trials (PRCT) comparing TPN vs TEN vs No treatment, or TEN vs no treatment. Although some of the studies have shown improvement in nutritional indices and other parameters (5,7,18,19,20), there is no dramatic effect on outcome. These studies are also inadequate to prove that nutritional support has no benefit at all. However, some evidence in patients with acute pancreatitis (3,6,7,13,14) and other disease processes (Trauma and sepsis) (21) suggests, that failure to achieve adequate nutritional support worsens outcome. It is not logical to starve patients beyond 5 to 7 days, especially, if the pre-existing nutritional status is not good and the disease runs a protracted course. Koretz suggests that one can wait for 10 to 15 days in critically ill patients (22). However, Koretz himself agrees that this long duration of starvation may not be advisable if there is pre-existing malnutrition (23). In general there is no definitive primary therapy for pancreatitis. The treatment is mainly supportive. Nutritional support should be an important component of this overall supportive care. Although its specific role in influencing the outcome is not known at present, use of nutritional support seems reasonable in patients with moderate to severe pancreatitis and especially if the pre-existing nutritional status is poor and the disease is likely to run a protracted course or if complications develop and/or operative measures are indicated.

Both Parenteral and enteral nutrition have been used in patients with complications with limited success (24,25,26,27). Placement of Nasojejunal tube may be difficult or impossible in the presence of pseudocyst or abscess. In addition enteral nutrition should be stopped if pain or ascites increases or pseudocyst increases in size. TPN is safer during this phase (7,24). "Nutrition support for patients with severe pancreatitis may prevent nutrient deficiencies, and preserve lean body mass and functional capacity when nutrient intake falls below needs" (28). The role of nutritional support is not a definitive therapeutic intervention, but is an adjunct to primary therapy, and is an essential component of supportive care in severe and complicated cases (6,7,28,29,30).

Objectives of nutritional support

In general, the objectives of nutritional support in acute severe pancreatitis are:

1) To maintain nitrogen balance or more often to minimise nitrogen imbalance, 2)To support the acute phase inflammatory response till the patient recovers and hypermetabolism resolves, 3) to preserve body functions that are functioning normally, and to facilitate recovery of those that are failing, 4) To prevent specific nutritional deficiencies.

Who needs nutritional support ?

This depends on:

1. pre-existing nutritional status
2. severity of the disease

The pre-existing nutritional status may be good or poor, and the disease may be mild or severe. The severity of the disease is assessed by Ranson's criteria, APACHE II Score and Dynamic CT scan Grade (Balthazar criteria, 31). Based on these two factors, there are three groups of patients (3,4,32):

Group I : Good nutritional status + Mild pancreatitis

Group II : Poor nutritional status + Mild pancreatitis

Group III : Good or Poor nutritional status + Severe pancreatitis

Group I patients without complications usually resolve in 5 to 7 days and do not require total parenteral nutrition (TPN), or total enteral nutrition (TEN) via a tube. Oral diet with less fat is considered safe to start with. However, there is no theoretical or practical support

for less fat. A well balanced, nutritious and balanced diet should be given (11). Too early return to full oral feeding may aggravate symptoms. Feeding should be gradually increased from day 5 to 7 (3,4). Group II and III patients need early nutritional support by parenteral and/or enteral route. In patients with poor nutritional status early nutritional support is safer as studies have shown that in patients with poor nutritional status, the acute phase response is only 40 to 50% of normally nourished patients (13,33).

When to start ?

Once the patient is haemodynamically stable with appropriate supportive therapy (approximately in 5 to 7 day's time), a definitive decision is taken to support the nutrition. The approximate expected length of stay can be assessed by the severity of disease, nutritional status, development of complications, and appropriate supportive therapy is planned. However, there is no place for aggressive nutritional support from day 1 as advocated by some authors (5,21,34).

Route of nutritional support

Until recently, TPN was considered as the gold standard in the management of severe pancreatitis (3,7,34,35,36). The aim being to 'put the gland to rest' (3,4,34,35,36). The major question is how pure is the gold in the standard?

Although bowel rest certainly decreases pain, no clinical trial has proven that it decreases the morbidity or mortality of the disease (4,15,23). The stimulation of the gland depends on the type of feed and the level at which it is delivered through the gastrointestinal tract. Oral normal diet causes maximum stimulation. Jejunal elemental diet causes minimal stimulation. TPN with or without fat produces the least or no stimulation (4,11,34,35,36,37). However, recent studies indicate that during an acute attack of pancreatitis the gland may not respond to any form of stimulation (11).

Currently, the trend is changing in favour of enteral nutrition. Intrajejunal elemental or semielemental diet is preferred whenever feasible. The single most advantage being cost (11,18,19,20,34,35,36,38). TEN may improve the gut barrier function and therefore may reduce bacterial translocation. This may reduce the development of systemic inflammatory response syndrome (SIRS), multisystem organ failure (MOF), and sepsis (39,40,41). However, at present no definitive conclusive evidence is available to show TEN is superior to TPN in preventing development of MOF and sepsis in acute stress states (42). Analysis of two recent PRCT studies claiming that TEN is superior to TPN does not clearly support their claims. Based on scoring system, initial CT score and laboratory findings, Windsor *et al* claimed that compared to parenteral nutrition, enteral nutrition decreases the acute phase inflammatory response and decreases disease severity. This study (20) includes mild to severe cases (only 13 out of 34 were severe cases). The average APACHE II score is higher in patients receiving TPN. In addition the main etiological factors causing pancreatitis is also different in those receiving TPN or TEN. Whether this will have any effect on the outcome has to be studied. The disease also seems severe in TPN treated group (3 out of 7 had surgery). In addition the number of patients with severe disease are small. From this limited study, it is difficult to conclude that administration of TPN adversely modulates the inflammatory response and outcome compared to TEN which favourably modulates it, as other studies have shown no advantage for TEN in critically ill septic patients(42).

Kalfarentzos, *et al* (18) claimed that enteral nutrition is superior to parenteral nutrition in acute severe pancreatitis. The numbers in this study were small. The pancreatitis related complications were higher in the TPN group. From the pathological description, it appears that the pancreatitis itself was more severe in the TPN group, with more cases having pancreatic necrosis. The serial CT grade is not available. The outcome in this study is probably due to the severity of the disease rather than due to TPN.

From these studies it is difficult to conclude that TEN is superior to TPN. However, these studies showed TEN is safe and as effective as TPN. Further prospective multicenter randomized controlled trials (PRCT) in a larger number of patients are needed. Because of the heterogeneous nature of the disease and the patients who develop it, it will be difficult to conduct a satisfactory randomized prospective study. The limitations are: 1) ethical concerns with randomizing patients to a control group without TPN or TEN, 2) heterogeneity of the variables influencing outcome, and 3) difficulty in stratifying patients according to degree of malnutrition, 4) obtaining adequate numbers. However, the evidence is more persuasive that in severe and/or protracted disease, especially in alcoholic patients with an already compromised nutritional status the prompt use of parenteral nutrition may well be crucial for survival, especially if complications occur or operative measures are indicated (12,13,14,30,35,36).

Review of the literature shows both advantages and disadvantages for TPN and TEN (6,7,12,15,35,43) (Table 1 & 2). Availability, cost, and expertise of the team will also influence the route of delivery. The cost of TEN is less compared to TPN. It is only marginally less in some series, if all the cost factors are taken into consideration. In one series the approximate cost of administering nasojejunal elemental feedings (US $ 1200 per week) is only minimally less than the cost of central

TPN (US $1400 per week). The cost estimates include professional fees for line placement, cost for diet delivery and expense of nutritional assessment and monitoring (3). In another study the cost for nasojejunal tube placement is US $600, and the cost of Central line placement is US $500 (44). The minimally higher cost of TPN is therefore not a viable argument against its use.

What type of parenteral nutrition products to be given and by what route?

In general central venous "aggressive" nutritional support with fat is commonly practised. The risk of sepsis is greater with central venous administration. Studies have shown that aggressive hypercaloric nutrition is not utilised well by critically ill patients, and may be harmful (45). Recently, the degree of hypermetabolism in critically ill adult and paediatric patients has been modified downward (45,46,47,48,49,50). Indirect calorimetric studies have confirmed that the previous estimated requirement (3000-4000 calories/24hour) was very high and actual measured resting energy expenditure is around 1400 calories/day in adults. The current recommendations for critically ill patients are: Total calories 25 kilocalories/kg/day. Water requirement : about 1mL of water per kilocalories administered is sufficient. 30 to 70% of the calories can be provided as glucose and 15 to 30% of total calories as fat. Protein should form 15 to 20% of the total calories. Approximately 1.2 to 1.5gm protein is sufficient at the start and may be increased to 2.0gm per kilogram if there is SIRS. BUN, blood sugar and serum triglycerides should be monitored (51).

What type of jejunal feeds to be used - semielemental or elemental ?

Though elemental feeds are believed to be absorbed better and pancreatic stimulation is probably less when compared to semi-elemental formulas, studies show semi-elemental feeds with low-fat are better utilised, and absorbed well, and the effect on pancreatic stimulation, is probably only marginal without any adverse effect on outcome (11,15,38,39). In addition, it costs less than elemental diet and is more easily available.

TPN or TEN ?

The question is not whether TPN is superior to TEN. Although the cost of enteral nutrition is relatively less, one may have to use both in the same patient due to the severity of the disease. Judicious use of both TPN and TEN is recommended, as this will avoid wastage of nutrients, and is more cost-effective. The advantages and disadvantages of both parenteral and enteral nutrition should be considered carefully in each patient (32).

Table I. Advantages and disadvantages of TPN

Advantages
1. Rapid ability to achieve goal calories
2. Relative ease of gaining accesses to peripheral or central venous route.
3. Lack of pancreatic stimulation
4. Avoidance of the proximal gut, which may be relatively obstructed by inflammatory mass or ileus.
Disadvantages
1. High cost
2. Failure to use the gut may be harmful
3. May exaggerate the stress response to pancreatitis
4. Increased incidence of line sepsis ?
5. Technical complications of central venous access
6. Increased frequency of hyperglycemia
7. Caution: Use of lipids - if there is hypertriglyceridemia

Table II. Advantages and disadvantages of TEN

Advantages
1. Minimal or insignificant stimulation of pancreas may not be harmful
2. Cost is less one third to one-fourth of TPN (marginal in some series)
3. May improve gut barrier function, improves mucosal nutrition, reduces bacterial translocation and may reduce SIRS, MOF and sepsis
Disadvantages
1. Placement of Naso Jejunal tube endoscopically or by fluoroscopy in a conscious, sedated critically ill patient is needed.
2. Not always successful.
3. Risk of aspiration in a patient who is not intubated
4. Proximal dislodgement of the tube may aggravate pancreatitis
5. Advancement to goal calories takes time.
6. If not tolerated, wastage of feeds is possible.

Based on this a practical clinical pathway for nutritional support is proposed. Although this pathway is proposed for acute pancreatitis, it is applicable to all critically ill patients.

Clinical pathway for management

With the present state of knowledge from the literature a Nutritional Support clinical pathway for acute pancreatitis is shown in Figures 1 and 2. The aims are to provide a rational approach to the patient with acute pancreatitis that is cost–effective and safe.

a) In Group II patients with mild pancreatitis, nutritional support is started from day 3 to 5 after carefully assessing the disease status and the need.

b) In severe pancreatitis with or without complications, starting parenteral nutrition with fat by peripheral route by 5 to 7 days is safer during the acute phase. The patient's progress is assessed frequently. After a period of 5 to 7 days a decision is made on whether to continue TPN or start TEN or to use both. If the patient is stable switching over to Jejunal feeds appears more appropriate and cost-effective (32).

When TPN or TEN is used, insulin supplementation may be needed. Hypertriglyceridaemia can occur and serum triglyceride levels should be monitored. If surgery is performed nasojejunal tube positioning is easier. In children, transpyloric jejunal placement, which is more secure and safer is preferred to surgical jejunostomy or needle-catheter jejunostomy (52,53,54). In adults complications have been reported in up to 25% with surgical or percutaneous jejunostomy procedures (39).

Though sepsis due to central line infection has been reported to be high with TPN patients, recent PRCT did not show any significant difference (55). In addition, catheter infection rate is high with triple lumen central lines (56). However, the overall incidence of sepsis is higher in acute pancreatitis, and it is believed to be due to neutrophil dysfunction and decreased phagocytosis by hepatic Kupffer cells (57,58). Peripheral parenteral nutrition with fat is a safe alternative, cost-effective and avoids central line associated sepsis.

In children pancreatitis is usually secondary to trauma, drugs (cytotoxics), viral infection or worm infestation. The severe cases are started on peripheral parenteral nutrition for 5 to 7 days followed by naso-duodenal or naso-jejunal semielemental or elemental diet for a week and gradually weaned off to oral feeds (2,52,53,54). If complications occur, either TPN or TEN as appropriate is provided for a longer time.

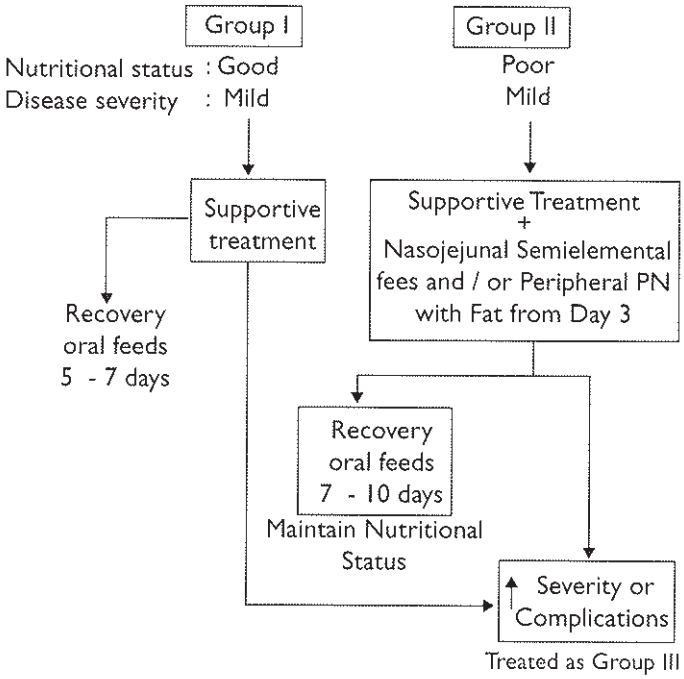

Fig 1. Clinical pathway for a practical approach to nutritional support in mild acute pancreatitis based on nutritional status and disease severity

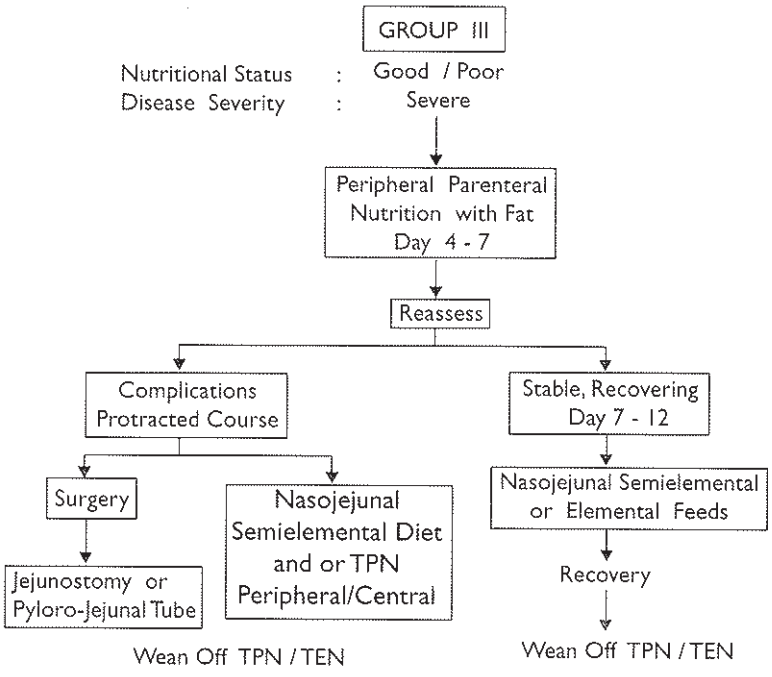

Fig 2. Clinical pathway for a practical approach to nutritional support in severe acute pancreatitis

Future trends

In future, substrate specific nutritional needs of the gut, liver and immune system, which act at cellular level, may be used to improve the outcome. Supplements like glutamine, branched chain amino acids, omega-3 fatty acids, dietary RNA (Immunonutrition) and modified structured lipids have been tried, but studies conducted so far have not substantiated any advantages of such substitutes (3,4,11, 59,60,61). The major questions in feeding the critically ill patients that still remain unanswered are:

1. How to feed the sick cell during acute stress? In

other words, how to supply what will be utilised by the sick cell?

2. Whether supply of nutrients improves the function of the sick cell or is it a recovering sick cell that is utilising the supplied nutrients more appropriately?

3. Whether nutrients have specific therapeutic value or are given for nutritive value?

Until these questions are answered specifically the place of nutritional support in acute severe stress states like sepsis or pancreatitis will remain controversial.

To obtain the real answer further strictly controlled multicenter prospective randomized trials are needed. This includes age range, type of center, hospitals with comparable facilities and patient care, using the same criteria, types of nutrient products supplied, etc. Age range is important because still we do not know whether the immune and metabolic response to acute stress is similar in a healthy 30-year-old and a 60-year-old patient. Are they comparable? In addition a study conducted in a Veterans hospital is not comparable to a study conducted in Mayo clinic and this is even less applicable to a hospital in Malaysia. We have to conduct our own PRCT, with adequate number of patients before any definitive conclusions can be arrived at for local patients.

Conclusion

Critical analysis of the literature shows that nutritional support in acute pancreatitis is essentially part of the overall supportive management and not a form of primary therapy. The question is not "how to feed the gland which is eating itself?", but to know "how to feed the whole organism safely?". At present initial peripheral parenteral nutrition and subsequent enteral feeding will be a safe, cost-effective, and practical approach when nutritional support is needed in acute pancreatitis.

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