

## Nutritional support in patients with acute pancreatitis

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## 1. ABSTRACT

Pancreatitis is a diffuse systemic immuno-inflammatory response to a localized process of auto-digestion within the pancreatic gland, caused by premature activation of proteolytic digestive enzymes. According to the ATLANTA criteria (1992) we recognized a mild and a severe acute pancreatitis (SAP). Mortality rate in SAP account up to the 20% and most complications and deaths are due to an inflammatory immune response to pancreatic necrosis and/or infection. Patients affected by SAP rapidly incur accelerated catabolism and thus nutritional support is essential, especially in the earliest period of the disease. Recent observations show that the route of nutritional support may also affect disease severity and its course. In this view several important questions about nutritional support need to be addressed: indication, timing, enteral vs parenteral and composition. With this review we analyze the state-of-the-art and we present a decisional flow chart to better manage the nutritional support in SAP.

## 2. INTRODUCTION

Clinical pancreatitis is a diffuse systemic immuno-inflammatory response to a localized process of auto-digestion within the pancreatic gland, caused by premature activation of proteolytic digestive enzymes. Unfortunately, the events that trigger the sequence of enzymatic reactions responsible for initiating acute pancreatitis remain unknown(1).

According to the 1992 Atlanta classification, Severe Acute Pancreatitis (SAP) can progress in two different stages. In the first one (7-10 days), which is initially sterile, a systemic inflammatory response syndrome (SIRS) with septic complications and multiple organ failure (MOF) may occur, leading to potentially fatal complications. In the second scenario, usually after the second week in the course of disease, local complications such as pancreatic necrosis may develop. In cases of infected pancreatic necrosis the patient's life is

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threatened(2). Most complications and deaths that occur in SAP are due to an inflammatory immune response to pancreatic necrosis and/or infection.

While the precise mechanisms that determine the overall severity of pancreatitis are not well defined, a number of clinical factors have been identified, which seem to correlate with disease severity. Presence of necrosis on computerized tomography (CT) scan is a major factor in determining disease severity and is mainly responsible for the degree of clinical 'toxicity', development of complications, and ultimately, overall survival. (3)

Failure of at least one organ or functional system is strictly associated with greater severity of disease (3). The serum levels of several inflammatory cytokines have also been associated with overall disease severity. Specifically IL 1, IL 6, IL 8, and TNF levels have been shown to correlate with disease severity of pancreatitis, and may even be used to predict end-organ failure, duration of hospital stay, and mortality (4). Patients affected by SAP rapidly incur accelerated catabolism and thus nutritional support is essential, especially in the earliest period of the disease. Recent observations show that the route of nutritional support may also affect disease severity and its course. Enteral feeding (via naso-jejunal tube) has been associated with less disease severity than parenteral feeding (via total parenteral nutrition) (5).

### 3. NUTRITIONAL ALTERATIONS DURING PANCREATITIS

Pancreatitis represents a wide spectrum of clinical diseases involving a diffuse inflammatory process of the pancreas with variable involvement of other regional tissues and/or remote organ systems (1). Patients with a mild disease account for approximately 80% of hospital admissions for pancreatitis (1,6,7).

These patients usually experience a self-limited hospital course and can normally be supported with intravenous fluid resuscitation, analgesia, and rapid return to oral diet. Severe pancreatitis differentiates from mild pancreatitis due to the presence of organ failure or evidence of necrosis on dynamic computerized tomography (CT) scan. This latter group accounts for 20% of hospital admissions for pancreatitis, tends to have a more prolonged hospital course with higher mortality, and is more likely to require nutritional hyperalimentation.

Nutritional support in the pancreatitis patient is both critical and complex, due to a number of factors that promote nutritional deterioration. The resulting metabolic response or stress state often increases protein and calorie requirements. Peri-oral ingestion of nutrients is often reduced by abdominal pain with food aversion, nausea and vomiting, gastric atony, and paralytic ileus, or by partial duodenal obstruction caused by pancreatic gland enlargement.

Even the carbohydrates and fat absorbed across the gut wall may not be fully utilized due to metabolism

errors and specific substrate intolerance. Excessive loss of protein may occur due to widespread inflammation of peritoneal and retroperitoneal surfaces, diarrhoea, or formation of pancreatic fistulas. The metabolism of acute pancreatitis involves a classic stress state shown in previous studies to be very similar to that seen in sepsis (8,9) and is characterized by hyperdynamic changes, hypermetabolism, and catabolism.

The hemodynamic changes include increased cardiac output, decreased systemic vascular resistance, and an increase in oxygen consumption, presumably related to the release of vasoactive kinins, proteases, and false neurotransmitters. In severe cases, oxidative metabolism may become impaired with oxygen consumption falling due to reduced oxygen extraction at the tissue level (10).. Hypermetabolism with increases in measured resting energy expenditure (REE) as high as 139% of the value predicted by the Harris-Benedict equation (HBREE) is seen in the majority of patients (11).

In general, a greater number of patients with acute pancreatitis will be hypermetabolic if compared to patients with chronic pancreatitis (61% vs 33% respectively) (11). Sepsis complicating pancreatitis may independently raise energy expenditure further. Catabolism and the proteolysis of skeletal muscle increase concentrations of aromatic aminoacids, decrease levels of branched-chain aminoacids, and accelerate ureagenesis. A number of nutritional alterations occur with an exacerbation of acute pancreatitis, with or without underlying chronic pancreatitis, as a result of errors in carbohydrate and fat metabolism (10,12). Errors in carbohydrate metabolism may result from increased cortisol and catecholamine secretion in the stress state, which lead to an increase in the glucagon/insulin ratio, impaired betacell function, and insulin-resistance. Gluconeogenesis is increased, while glucose clearance and oxidation is diminished.

In acute episodes of pancreatitis, pre-existing ethanol abuse, massive fluid shifts, and problems with malabsorption can increase predisposition to micronutrient deficiencies.

Errors in fat metabolism occur less frequently. Lipolysis and lipid oxidation are usually increased (7,10,13) but clearance from the blood can be reduced, resulting in hyperlipidemia (and particularly hypertriglyceridemia) in 12 - 15% of cases (10,14,15).

Hypocalcemia occurs most often in as many as 25% of patients (15), presumably related to decreased parathyroid hormone secretion, increased stimulation of calcitonin, hypomagnesemia, hypoalbuminemia, and saponification of calcium with free fatty acids (10).

Patients with pancreatitis typically require a total of no less than 2500 calories/day as estimated by indirect calorimetry. The calorie:nitrogen ratio should be approximately 100:1, and hence total protein supplied should be between 2 and 2.5 g/kg/day. Total lipids should

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not generally exceed 1.5 g/kg/day (16).

The most important aspect when considering nutritional therapy is determining the severity of the pancreatitis. Patients who present severe pancreatitis have more prolonged gastric and duodenal atony, are less likely to progress to oral diet within five days, are at greater risk for complications, are more likely to require at least one operation, and have a higher associated mortality rate when compared to patients with mild pancreatitis (27% vs 3%, respectively) (14).

The APACHE II scoring system and the time honoured Ranson criteria are useful for differentiating severe from mild pancreatitis early in the patient's course.

Evidence of organ failure on clinical presentation and pancreatic necrosis on dynamic CT scan are even more important factors in determining severity of pancreatitis and are probably the two greatest indicators of patient outcome. In the absence of organ failure, pancreatitis is invariably mild. However, when the course of pancreatitis is complicated by the failure of at least one organ system, the mortality jumps from almost 0% to 19% (3). The presence of necrosis on CT scan raises the mortality from, 1% (seen in uncomplicated interstitial pancreatitis) to upwards of 10%. An APACHE II score of 10 in a patient with 3 Ranson criteria provides a strong suggestion of necrotizing pancreatitis(3).

The most ironic aspect of nutritional support in pancreatitis is the presumed need to "rest the pancreas". Although the concept that pancreatic stimulation is counterproductive to solving the inflammatory process (12) has physiological sense, the need for pancreatic rest in acute or chronic pancreatitis, surprisingly, has never been proven. Furthermore, the definition of pancreatic rest is variable. Of the three components, protein enzyme output is thought to be responsible for the autodigestion of the gland and perpetuation of the inflammatory process.

The most important point is that the entire scheme of pancreatic secretion involves gut luminal stimulants, and the evidence that similar stimulation can come from intravenous nutrients is controversial.

An increasing body of evidence suggests that the gut plays an important role in the immune and inflammatory response to SAP. Experimental data suggest that the endogenous cytokines involved in this response are stimulated by endotoxin and other bacterial products absorbed by a metabolically altered intestine (14). Several studies in patients with severe trauma and burns have shown that total enteral nutrition (TEN) significantly diminishes the acute inflammatory response phase and the incidence of septic complications when compared to total parenteral nutrition (TPN) (12). The suggested mechanism of this response is that feeding through the gut would maintain the intestinal barrier function, thus precluding bacterial and toxin translocation from the intestinal lumen.

In reviewing current literature, several important

questions need to be addressed regarding nutritional support in pancreatitis. Does providing nutritional support, compared to no nutrition, make a significant difference in clinical outcome? If nutritional support is preferable to no nutritional therapy, what is the optimal timing for initiating that support? Does the route of nutritional support (enteral vs parenteral) have an impact on patient outcome? Does the composition of the nutritional support affect clinical sequelae? Unfortunately, there are only four prospective randomized studies in current literature evaluating nutritional support in pancreatitis (5,17,18,19).

## 4. TOTAL PARENTERAL NUTRITION VS ENTERAL NUTRITION

Acute pancreatitis is a catabolic hypermetabolic disease process in which the risk for deterioration of nutritional status is very high. Oral intake may be reduced for prolonged periods due to the presence of ileus, gastric atony, nausea, vomiting, and pain. Multiple factors exist which promote a net negative energy and protein balance, and include increased energy demand, decreased intake of exogenous nutrients, decreased assimilation of ingested nutrients, increased protein losses across inflamed mucosal surfaces, and therapy designed to restrict nutrient intake. Deterioration of nutritional status adversely affects host defence, immune competence, and ability to resist nosocomial infection, which so often complicates the course of pancreatitis.

Micronutrient deficiencies and protein calorie malnutrition seen in chronic ethanol abuse may be exacerbated by the development of pancreatitis. A small subset of patients (< 20%) will go on to have severe pancreatitis, associated with a protracted course and greater likelihood for organ failure, systemic inflammatory response syndrome, need for surgery, and failure to reach an oral diet within 7 days (3,20). Failure to achieve adequate nutritional support may worsen the outcome, as suggested by one study where pancreatitis patients with a persistently negative nitrogen balance had a higher mortality than patients who did not. Surprisingly, a fairly good argument can be made for providing no nutritional support to patients with acute pancreatitis (21).

The clinical manifestations of acute pancreatitis represent a systemic immuno-inflammatory process in which starvation may be the most appropriate, natural, physiologic response to that injury. Feeding the patient and providing exogenous nutrients may alter that response in ways which are not 'natural', and thereby jeopardize the outcome (22,23).

Minimal data exists to justify nutritional support in acute pancreatitis and no prospective randomized control trials exist to show that early nutritional support reduces the duration or lessens the severity of the disease process when compared to patients receiving no nutritional therapy (22). Early nutritional support is associated with complications. In the only prospective randomized study of early nutritional support, the study group receiving total parenteral nutrition (TPN) remained in hospital almost 1

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week longer than the control group who received no nutritional therapy (17).

Nutritional support has been implicated as a cause of pancreatitis itself, as documented by studies in which hypercalcemia (24) or hypertriglyceridemia (25,26) resulting from TPN led to pancreatitis in patients with other disease processes.

Early return to oral diet or displacement of the jejunal feeding tube back into the stomach may lead to exacerbation of the disease process in pancreatitis patients who otherwise appear to be convalescing uneventfully (18).

Clearly, the majority of patients (< 80%) with mild severity of disease, will do well regardless of whether nutritional support is provided, and are likely to return to oral diet quickly within 7 days (3,20).

Traditionally, TPN was the preferred route of nutrition support in acute pancreatitis, the objective being to give the pancreas a rest (27). Other objectives of the symptomatic treatment of severe acute pancreatitis are pain relief, fluid and electrolyte replacement, and management of cardiovascular, respiratory, renal, and metabolic complications (16).

Unfortunately, TPN can be associated with complications. They include mechanical problems (malfunctioning pump, administration sets or tubing, catheters), infections (catheter related sepsis), and metabolic disturbances (electrolyte and acid-base abnormalities, hepatic dysfunction, etc.). In contrast to TPN, EN offers some advantages.

It preserves gut mucosal integrity and maintains proper immune functions, minimizing or preventing bacterial translocation in the gastrointestinal tract (28).

In addition, EN is associated with fewer septic complications after traumatic or surgical injury (29,30). The cost of EN can also be less than that of TPN (14,31).

Many enteral feeding formulas are available, such as standard or "intact protein" products and blenderized formulas. These diets require digestion for adequate absorption and therefore are expected to stimulate pancreatic functions.

Some EN products were developed specifically for patients with impaired digestion and are commonly called elemental. These products also are called chemically defined and partially hydrolyzed formulas (32). In elemental products, proteins are hydrolyzed to small peptides and free amino acids. Carbohydrates like maltodextrin and hydrolyzed or modified starch are provided. Fat sources vary among manufacturers, but in all elemental formulas, fat content is very low, usually less than 6% of total calories from long-chain fatty acids. Some formulas also contain medium-chain triglycerides and short-chain fatty acids, which together with small peptides allow for ease of absorption with minimal pancreatic

stimulation or secretion.

Improved endoscopic techniques for feeding plus advances in enteral product formulation have led to greater tolerance of EN in patients with disease states formerly thought to require TPN. The relationship between site of tube feeding (stomach, duodenum, jejunum) and degree of pancreatic stimulation still requires clarification.

The key problem with the pathophysiologic disease process of pancreatitis, is the production of proteolytic enzymes which determine a self-digesting process of the gland. The need to reduce the stimulation and secretion of these proteolytic enzymes seems paramount to reversing or halting the disease process.

Reduced pancreatic protein synthesis and secretion should be expected to alleviate pancreatic inflammation, minimize complications, and accelerate the recovery rate.

Parenterally infused nutrients should have the least likelihood of stimulating an inflamed pancreatic gland. Target calorie infusion may be achieved quickly and easily with TPN. Tolerance and assimilation of parenterally infused nutrients would be expected to be much greater than nutrients infused into the gut in the face of ileus, nausea, vomiting, segmental dysmotility, and a gut luminal environment devoid of pancreatic enzymes. Gaining and maintaining access to the vascular space is easily obtained by most intensive and general surgeons, while obtaining gut access below the Ligament of Treitz is a skilled endoscopic procedure and the appropriate expertise may not be available at all medical centres. Patient compliance would be expected to be better with total parenteral nutrition, as patients are usually more willing to have intravenous access placed than a nasoenteric tube placed through the nose.

Therapeutic efforts to avoid pancreatic stimulation and protein enzyme secretion may not be as important as previously thought. A number of studies have shown that pancreatic exocrine secretion is severely reduced in patients shortly after the onset of acute pancreatitis. Cholecystokinin-stimulated secretion is almost completely abolished at the time of maximal histologic damage to the pancreas, and may take several months following the attack to return to normal. Recovery of secretory ability takes longer after severe necrotizing pancreatitis rather than after edematous pancreatitis.

Pancreatic secretory response to direct stimulation by a pharmacologic agent (such as secretin) may appear to return sooner than the response to more physiologic stimuli (such as the Lundh meal). Any other therapeutic means to inhibit pancreatic secretion have been unsuccessful in altering patient course, including treatment with atropine, cimetidine, glucagon, calcitonin, somatostatin, and nasogastric aspiration. The early benefit of decreased pancreatic stimulation may only be pain relief. Increased pain with early re-feeding is usually well tolerated and leads to exacerbation of the disease process in

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only a small percentage of patients. Pancreatic rest is poorly defined and not easily evaluated in the clinical setting. Any stimulation of the pancreas that occurs is multi-factorial (33). Feeding low in the gastrointestinal tract with elemental formulae (which are nearly fat free and have hydrolyzed protein) may invoke a degree of stimulation that differs little from parenteral nutrients.

Decreasing pancreatic stimulation to subclinical levels of secretion may allow resolution of the disease process, and complete reduction of protein enzyme output to basal unstimulated levels may not be required.

Gut integrity may be a much more critical issue contributing the overall severity of pancreatitis, and may be a significant factor in the development of late complications (34,35,36).

Gut atrophy and loss of villi does occur in humans in response to pancreatitis, and feeding by the enteral route has been shown to blunt atrophy and maintain villous height. An atrophic gut in acute pancreatitis may be a source for systemic endotoxin exposure and bacterial sepsis. Bacterial translocation from a leaky gut may be capable of infecting the pancreas and parapancreatic tissues.

Gut atrophy has been shown in humans to generate cytokines and other inflammatory mediators, worsening oxidant stress, hypoglycemia, physiological stress, and the systemic inflammatory response syndrome associated with pancreatitis. Enteral feeding compared to parenteral nutritional support is associated with lower cost and fewer complications of hypoglycemia, central line sepsis, and overall infectious complications (37,38,39,40).

## 5. GUIDELINES

The Guidelines have been prepared in order to help physicians to diagnose acute pancreatitis accurately and to manage patients by means of an appropriate treatment policy, thus improving survival rates. Several sets of evidence-based guidelines for the management of acute pancreatitis have been published; those of the Atlanta Symposium of 1992 (1), the United Kingdom Guidelines of 1998(2) and the Santorini Consensus Conference of 1999 are representative.

However, they were based on the evidence available at the time, and the validity of any set of guidelines is short-lived and guidelines need to be revised every 2 years (1).

Indeed, new evidence is reported almost daily, and guidelines for management in clinical settings are changing nearly as fast, thanks to the remarkable advances in medical equipment and treatment techniques developed in recent years. The International Association of Pancreatology Guidelines (41) were most recently published in 2002, but they are concerned solely with the surgical management of acute pancreatitis.

The Guidelines Publishing Committee very much hopes that this publication will help clinicians worldwide to become familiar with the Guidelines, and the Committee hopes that those professionals will offer their comments and criticisms once they have had the opportunity to compare them with the guidelines in use in their own countries.

The patients most likely to benefit from aggressive nutritional support are those with a severe pancreatitis, probably defined by  $\geq 3$  Ranson criteria and an APACHE II score of  $\geq 10$  (3,20). In these patients, enteral access should be obtained within 48 hrs of admission and feedings begun via a nasojejunal tube. Although no optimum formula has been identified, elemental or semi-elemental formulae with the lowest concentration of long chain fat and protein in the form of small peptides or individual amino acids may theoretically lead to less stimulation of the pancreas. Probably any formula infused into the jejunum, however, should lead to clinically insignificant levels of stimulation (43).

When possible, energy requirements should be measured by indirect calorimetry. Feedings based on estimate equations should be conservative to avoid overfeeding. Close attention to tolerance is important and the patient should be monitored for evidence of partial ileus, diarrhea, and metabolic complications of hyperglycemia and hypertriglyceridemia.

Patients with severe pancreatitis in whom enteral access cannot be achieved, or in whom intolerance or clear exacerbation of the disease process occurs in response to enteral feeding, should be considered for total parenteral nutrition.

Initiation of TPN, however, should be delayed for 5 days after admission, past the point of peak inflammation, to avoid exacerbation of the stress response (43). Fat should comprise no more than 15–30% of the non-protein calories, and the TPN should be advanced only as fast as tolerance (i.e. hypertriglyceridemia and hyperglycemia) can be controlled.

Again, caloric requirements should be measured if possible by indirect calorimetry or provided in conservative amounts if based on estimate equations (to avoid overfeeding). Close attention to fluid volume resuscitation and electrolyte abnormalities should be maintained.

Patients with mild to moderate pancreatitis, as suggested by  $\leq 2$  Ranson criteria or an APACHE II score of  $\leq 9$  probably do not require aggressive nutritional support (3,20).

These patients may be managed simply with i.v. fluid resuscitation and analgesia. If a late complication develops, or if they are unable to achieve advancement to oral diet by day 7, they should be considered for aggressive nutritional support via nasojejunal tube or TPN.

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Need for operative intervention, or the development of a complication of pancreatitis (including ascites, pseudocysts, or fistula) does not necessarily alter the overall management algorithm. Certainly, clinical judgement and close monitoring of patient response to the initiation of nutritional support is important in deciding which route, which formulation, and which particular nutrient composition are required for an individual patient. As experience with enteral feeding in acute pancreatitis grows, fewer patients are likely to require feeding by the parenteral route.

Nutritional support was not considered in the previous UK guidelines. The Santorini consensus and the World Association guidelines comment on five studies that demonstrate the safety of enteral feeding in patients with acute pancreatitis<sup>(44)</sup>.

There is no benefit from enteral feeding in mild pancreatitis, and these patients do not need any dietary restrictions (45). Artificial feeding may be used in acute pancreatitis either to prevent complications or to provide long term nutritional support.

In patients with severe disease, oral intake is inhibited by nausea; the acute inflammatory response is associated with impaired gut mucosal barrier function. It has been suggested that nutritional support may help to preserve mucosal function and limit the stimulus to the inflammatory response. In these circumstances enteral feeding seems to be safer than parenteral feeding, with fewer septic complications (5,19). It is also cheaper.

These findings are supported by a further small study which demonstrated minor clinical advantages in recovery time in patients who received early enteral nutrition compared to those receiving parenteral nutrition (46). However, another randomised comparison, of enteral feeding versus no nutritional support, failed to demonstrate any effect of enteral feeding on markers of the inflammatory response (47).

The use of enteral feeding may be limited by ileus. If this persists for more than five days, parenteral nutrition will be required.

Various formulations have been used in pancreatitis, but no comparative studies exist to determine the relative merits of standard, partially digested, elemental, or "immune enhanced" formulations.

The majority of studies have reported enteral feeding via a nasojejunal tube; there is some evidence that nasogastric feeding may be feasible in up to 80% of cases (48). Caution should be used when administering nasogastric feeding to patients with impaired consciousness because of the risk of aspiration of refluxed food (49,50). The evidence is not conclusive to support the use of enteral nutrition in all patients with severe acute pancreatitis. However, if nutritional support is required, the enteral route should be used if that can be tolerated (grade A).

The nasogastric route for feeding can be used as it appears to be effective in 80% of cases (grade B) (44,51).

## 6. NUTRITIONAL ALGORITHMS IN ACUTE PANCREATITIS

The first step in management is to determine which patients have evidence of severe pancreatitis that may go on to require aggressive nutritional support. An APACHE II score of  $\leq 9$  patients with  $\leq 2$  Ranson criteria would identify that group with mild pancreatitis who are not likely to benefit from nutritional hyperalimentation. These patients should progress to *per os* diet within five days and should show rapid resolution of symptoms and the inflammatory response. Failure to improve within 48 / 72 hrs from admission in these patients should prompt a work-up looking for evidence of complications (1). On the other hand, those patients found to have an APACHE II score of  $\geq 10$  with  $\geq 3$  Ranson criteria, identify a group at high risk for complications who will most likely require nutritional hyperalimentation(7). Patients should be evaluated for evidence of multiple organ failure, and a dynamic CT scan should be obtained to look for evidence of pancreatic necrosis (52).

Of those patients determined to have severe pancreatitis, early enteral access should be achieved fluoroscopically or endoscopically with a naso-intestinal tube placed at or below the ligament of Treitz. Enteral infusion may be started with a fat-free elemental formula or small peptide semielemental formula. Patients should be monitored very closely for evidence of tube migration as well as evidence of intolerance, such as high residual volumes, nausea/vomiting, diarrhea, or aspiration of feeding formula. Patients should receive adequate analgesia to control pain.

There should be aggressive fluid resuscitation and repletion of micronutrients. Patients should be monitored in the ICU and possibly placed on broadspectrum antibiotics. Progression to TPN should be performed in patients who demonstrate clear-cut intolerance or who show increasing pain with significant increases in amylase and lipase on enteral feeding. Patients should be watched closely for hyperglycemia.

Triglyceride levels should be checked before and after the start of infusion.

The number of issues related to etiologic factors, pattern of complications, and treatment necessitate a multidisciplinary team approach to the management of patients with pancreatitis. The nutritionist needs to work closely with the surgeon, gastroenterologist, intensivist, and primary care physician to correctly assess the severity of illness, identify nutrient deficiencies, and anticipate metabolic complications from the disease process. Such combined effort will help the patient more rapidly resolve the acute inflammatory process and reduce the likelihood of long-term complications.

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