

NUTRITIONAL MANAGEMENT IN ACUTE AND CHRONIC PANCREATITIS



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Learning Objectives

1. Evaluate the classification, clinical manifestations, and long-term risks associated with acute and chronic pancreatitis.
2. Assess common diagnostic tools used in acute and chronic pancreatitis and evaluate their usefulness.
3. Analyze patient-specific characteristics in determining the nutritional support needs and goals of patients with acute and chronic pancreatitis.
4. Demonstrate an understanding of the role of enteral and parenteral nutrition support in managing acute and chronic pancreatitis.
5. Develop a plan to provide nutrition support through an appropriate route to a patient with acute and chronic pancreatitis.

Introduction to Acute and Chronic Pancreatitis

Epidemiology of Acute and Chronic Pancreatitis

Acute pancreatitis is defined as an acute inflammatory process of the pancreas with variable involvement of other regional tissues and remote organ systems. It is a relatively common disease, affecting 200,000 individuals annually in the United States. Although it often runs a mild course, up to 30% of acute pancreatitis cases will be associated with significant morbidity and mortality. Acute pancreatitis is characterized by the sudden onset of severe epigastric pain, which accounts for 3% of hospital admissions for abdominal pain. Mild attacks account for 70–80% of acute pancreatitis

admissions. The remaining 20–30% of patients are admitted with severe pancreatitis with reported mortality rates of up to 25–30%. Therefore, the ratio of mild to severe acute pancreatitis is about 4:1.

Acute fluid collection occurs in 30–50% of acute pancreatitis cases and typically resolves spontaneously. A pseudocyst is a fluid collection that persists for 4–6 weeks and becomes encapsulated by a wall of fibrous or granulation tissue. Asymptomatic pseudocysts do not require treatment. If symptomatic, pseudocysts can be managed surgically, radiologically, or endoscopically. A small subset of patients with severe acute pancreatitis will develop chronic pancreatitis or pancreatic necrosis. It is estimated that about 5–15% of patients with acute and chronic pancreatitis develop necrotizing pancreatitis. Necrotizing pancreatitis is a devastating disease with reported mortality rates of up to 50–80%. Appropriate surgical, antibiotic, and nutritional management reduces these rates to about 5–20%.

Classifying and Diagnosing Pancreatitis

Many scoring systems have evolved to identify patients with severe pancreatitis who are at highest risk for organ failure and/or local complications, such as necrosis, abscess, or pseudocyst. Ranson criteria are scored based on 11 clinical criteria with prognostic importance and is the most widely recognized system for classifying pancreatitis. Five of these criteria are measured at the time of admission and the other six in the first 48 hours after admission. The number of Ranson criteria present at the time of assessment

Fang J, DiSario JA. Nutritional management of acute pancreatitis. *Curr Gastroenterol Rep* 2002;4:120–7.

Retally CA, Skarda S, Garza MA, Schenker S. The usefulness of laboratory tests in the early assessment of severity of acute pancreatitis. *Crit Rev Clin Lab Sci* 2003;40:117–49.

Abbreviations in this Chapter

APACHE II	Acute Physiology and Chronic Health Evaluation II
CRP	C-reactive protein
EN	Enteral nutrition
TPN	Total parenteral nutrition

is correlated with the incidence of systemic complications and the presence of pancreatic necrosis. In addition to the Ranson criteria, the Glasgow criteria are scored using a similar approach with only eight clinical criteria assessed during the first 48 hours. These scoring systems are detailed in Tables 1-1 and 1-2. Mild acute pancreatitis is associated with two or fewer criteria with both the Ranson and Glasgow scoring systems. Despite some limitations in sensitivity and specificity, studies suggest that patients with a Ranson or Glasgow criteria of 3 or higher have severe pancreatitis.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) is an illness severity score and prognostic indicator based on 12 physiological variables, the patient's age, and any history of severe organ system dysfunction or immunocompromised state. Traditionally, an APACHE II score of 10 or higher indicates the presence of severe pancreatitis. However, many clinicians and researchers currently use a lower APACHE II score (6 or higher) to differentiate mild acute pancreatitis from severe acute pancreatitis. This lower APACHE II score has not yet been fully adopted by all practitioners because of the increased probability of erroneous classification of patients with mild acute pancreatitis as severe. The distinction between APACHE II scoring cutoffs and the classification of mild and severe acute pancreatitis is important in properly evaluating the results of clinical data from recently published studies. Studies that classify severe acute pancreatitis in patients with an APACHE II score of 10 or greater than three Ranson criteria ensures the exclusion of patients with mild disease. Unlike the Ranson or Glasgow system, the APACHE II score is more flexible, allows for classification of illness severity on admission, and may be recalculated daily. A combination of the APACHE II with either the Ranson or Glasgow scoring systems in research and clinical practice ensures sensitivity and specificity in classifying acute pancreatitis and assessing progression of the disease. To ensure the inclusion of patients with severe pancreatitis, studies should include only patients with three or more Ranson criteria or an APACHE II score of 10 or more.

In many institutions, measurement of biochemical markers has become a standard for prognostic assessment. An advantage of the markers is that they can be measured repeatedly and thereby draw attention to the development of severe disease more simply than the complex scoring criteria. The use of C-reactive protein (CRP) can detect pancreatic necrosis in the majority of patients with concentrations more than 120 mg/L. Increases in CRP

during acute pancreatitis occur with a delay of 1–2 days, as it reflects the stimulation of hepatic synthesis of the acute phase reactants mediated by interleukin-6. Although the release of inflammatory mediators such as interleukin-6 and polymorphonuclear elastase occurs more rapidly, serum CRP determination is still the most widely used individual marker for prognostic assessment of acute pancreatitis because of ease of use and widespread availability. C-reactive protein indicates pancreatic necrosis within 48–72 hours after disease onset with an accuracy of about 90%.

The Atlanta classification is an additional scoring system that uses information obtained by contrast-enhanced computed tomography and clarified definitions of the different complications likely to be encountered with acute pancreatitis. The Atlanta classification system categorizes disease under the general heading of pancreatic necrosis. Ultrasound or magnetic resonance pancreatography combined with this system aid in distinguishing among localized collections of necrotic tissues, acute pseudocysts, and fluid collections.

Evidence on computed tomography of hypoperfusion correlates well with pancreatic necrosis. Computed tomography is useful for diagnosing pancreatic necrosis after the first 24 hours of symptom onset with sensitivity further improving to about 100% between 4 and 10 days after symptom onset.

Interleukins (i.e., interleukin-6, interleukin-8, and interleukin-18), trypsin activation peptide, procalcitonin, procarboxypeptidase-activation peptide, and phospholipase A₂ also are markers of disease severity with proven validity, but they are either too expensive or too time-consuming for routine clinical practice. A single serological marker with absolute reliability to predict a severe attack of acute pancreatitis at any time after onset of the disease is still not available.

Amylase and lipase are both enzymes released from the pancreas during acute pancreatitis. Despite widespread use of amylase and lipase concentrations for diagnosing acute pancreatitis, the prognostic ability of either enzyme to assess severity of disease has been consistently poor. The reason plasma concentrations of the pancreatic enzymes have no value in predicting severity probably relates to the rapid decline in concentrations after an early peak. The peak occurs within the first 24 hours of symptoms, with amylase having a shorter half-life compared to lipase. The decrease in concentrations over the course of several days limits the accuracy of these enzymes in measuring pancreatic severity through the course of the disease. In addition, in the absence of pancreatitis, serum lipase may increase up to 2-fold above normal in severe renal insufficiency (creatinine clearance of 20 ml/minute or less). Pancreatic enzyme concentrations also have limited value in diagnosing chronic pancreatitis, with concentrations often normal or low. The diagnosis of chronic pancreatitis is based on recurrent abdominal pain, radiographic abnormalities, and functional testing failures. Practitioners traditionally have monitored daily enzyme concentrations instead of patients' overall clinical picture in patients with chronic pancreatitis. However, published data would suggest that this practice is unwarranted, and that patients' overall clinical presentation

Table 1-1. Ranson Criteria for Pancreatitis Severity

Ranson Criteria	
Assessed at admission	
Age	55 years or older
White blood cell count	Greater than 16,000 cells/mm ³
Glucose	Greater than 200 mg/dl
Lactic dehydrogenase	Greater than 350 IU/L
Aspartate aminotransferase	Greater than 250 IU/L
Assessed during initial 48 hours	
Hematocrit decrease	Greater than 10%
Blood urea nitrogen increase	Greater than 5 mg/dl
Calcium	Less than 8 mg/dl
Arterial PaO ₂	Less than 60 mm Hg
Base deficit	Greater than 4 mEq/L
Fluid sequestration	Greater than 6 L

PaO₂ = partial pressure of oxygen.

Ranson criteria is obtained by evaluating for the presence of 11 clinical criteria (five criteria are measured at the time of admission and the other six in the first 48 hours after admission). Each criteria is given 1 point. These criteria are added, with the sum total of these criteria equaling the Ranson criteria.

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should dictate chronic pancreatitis management.

A combination of tools has been suggested as a strategy to improve the distinction between mild and severe acute pancreatitis, early after disease onset. A retrospective analysis performed in 72 nonconsecutive patients with acute pancreatitis (32 severe) using a stepwise discriminant function analysis, selected a polymorphonuclear elastase value on day 1 and CRP value on day 2 as the best diagnostic combination. Researchers described 97% accuracy in predicting severe cases with this approach. However, their report does not clearly define specific cutoff values for polymorphonuclear elastase and CRP at these time points. Although polymorphonuclear elastase appears to be a useful tool for diagnosing acute pancreatitis, the availability of the test currently is limited to major research centers with limited availability in the community hospital setting.

Etiology and Clinical Manifestations of Pancreatitis

The causes of acute pancreatitis can be divided into several broad categories, including biliary obstruction, toxins, trauma, infections, vascular and metabolic abnormalities, and miscellaneous causes. The vast majority of cases are caused by biliary obstruction secondary to gallstone formation or toxins such as ethanol. In fact, biliary obstruction by gallstones accounts for about 45% of cases, and ethanol accounts for another 35%. The remaining 20% of cases are idiopathic or have miscellaneous causes.

Obstruction leads to increased pressure and distention in the pancreatic duct. Direct toxins (e.g., ethanol and other drugs), hypertriglyceridemia, and hypercalcemia can all

Table 1-2. Glasgow Criteria for Pancreatitis Severity

Glasgow Criteria	
Assessed during initial 48 hours	
Age	55 years or older
White blood cell count	Greater than 15,000 cells/mm ³
Glucose	Greater than 200 mg/dl
Albumin	Less than 3.2 g/dl
Arterial PaO ₂	Less than 60 mm Hg
Calcium	Less than 8 mg/dl
Lactate dehydrogenase	Greater than 600 IU/L
Blood urea nitrogen	Greater than 45 mg/dl

PaO₂ = partial pressure of oxygen.

Glasgow criteria is obtained by evaluating for the presence of eight clinical criteria in the first 48 hours after symptom onset. The sum total of these criteria is equal to the Glasgow criteria.

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stimulate the pancreas and activate zymogen granules. This process results in the activation of cytolytic enzymes, which initiate a cascade of inflammatory responses. These inflammatory responses lead to a spectrum of pancreatic injuries that range from mild edema to necrosis. The exact triglyceride concentration threshold associated with pancreatitis has not been definitely established. However, triglyceride concentrations of more than 1000 mg/dl are considered a risk factor for pancreatitis. It is important to note that triglyceride concentrations of 500–1000 mg/dl also may induce acute pancreatitis.

Acute pancreatitis usually has a rapid onset manifested by upper abdominal pain, vomiting, fever, tachycardia, leukocytosis, and elevated serum concentrations of pancreatic enzymes. The most prevalent feature of chronic pancreatitis is abdominal pain. This pain typically increases after a meal as a result of pancreatic acinar cell secretion activated by the hormone cholecystokinin.

Significant ischemia of the gland predisposes it to severe hemorrhage and necrosis. Necrotic pancreatic tissue presents a welcoming environment for microorganisms, with necrotizing pancreatitis leading to secondary infections in 40–60% of cases. Early studies reported mortality rates of 50–80% with necrotizing pancreatitis, but modern intensive care management has reduced mortality rates to about 20%. The high mortality rates associated with necrotizing pancreatitis are attributed to a severe systemic inflammatory response triggered by an intense cytokine reaction resulting in multiple organ failure. The organs most commonly affected are the lungs (e.g., adult respiratory distress syndrome) and kidneys (e.g., acute renal failure).

Nutritional Pathophysiology in Pancreatitis

Nutritional Pathophysiology in Acute Pancreatitis

Knowledge of the metabolic pathophysiology of acute pancreatitis is the foundation of appropriate nutritional management. Acute pancreatitis starts within the pancreas, with severe disease leading to extensive tissue destruction

generating profound systemic and metabolic derangements. These changes occur because of the release of hydrolytic enzymes, toxins, and cytokines, which damage several organ systems and promote hypermetabolism with a negative energy balance. Metabolism in patients with acute pancreatitis typically behaves in a similar fashion to patients with sepsis, with hyperdynamic changes, hypermetabolism, and catabolism. Patients with severe acute pancreatitis may develop hyperdynamic states, with increased cardiac output, decreased systemic vascular resistance, and mild to severe deficiencies of oxygen extraction.

Alterations in measured energy expenditure have been determined by indirect calorimetry and compared to predicted energy expenditure estimated using the Harris-Benedict equation in a prospective, case-referent study in 48 patients with pancreatitis (eight mild acute, five severe acute, 24 chronic, seven acute with sepsis, and four chronic with sepsis). Ranson criteria of three or more were used to classify severe acute pancreatitis. Researchers found a great deal of variability in measured energy expenditure with 10% of all patients hypometabolic (less than 90% of predicted energy expenditure), 38% normal metabolic (90–110% of predicted energy expenditure), and 52% hypermetabolic (more than 110% of predicted energy expenditure). There was a higher mean measured energy expenditure, expressed as percentage of predicted energy expenditure, for patients with sepsis with pancreatitis ($120 \pm 11\%$) compared with patients with chronic pancreatitis ($105 \pm 14\%$; $p < 0.05$). However, there was no significant difference in the mean measured energy expenditure for patients with sepsis compared with patients with acute pancreatitis ($112 \pm 17\%$; $p = \text{NS}$). In addition, patients with severe acute pancreatitis had a significantly higher mean measured energy expenditure ($126 \pm 10\%$) compared with patients with mild acute pancreatitis ($111 \pm 15\%$; $p < 0.03$). The variability makes it somewhat difficult to pinpoint the optimum caloric requirements of these patients, particularly with the Harris-Benedict equation. Therefore, recommendations for total caloric intake range from 25 kcal/kg/day to 35 kcal/kg/day in most patients. The upper limit of this calorie range is best in patients with sepsis coinciding with severe acute pancreatitis. The most accurate means of determining caloric requirements is through indirect calorimetry.

Acute pancreatitis increases the catabolism and proteolysis of skeletal muscle by as much as 80% in comparison with healthy controls. Further nitrogen losses increase to as much as 20–40 g/day. Decreased concentrations of total plasma proteins, rapid turnover of proteins, and a marked decrease of the ratio of branched-chain to aromatic amino acid further characterize this hypercatabolic state. Theories regarding this ratio have led to a handful of small studies evaluating exogenous administration of branched-chain amino acids (e.g., L-arginine) with no role defined. Therefore, exogenous standard amino acid mixture administration is the mainstay of therapy in patients with pancreatitis. Significant decreases in plasma essential amino acids, with marked reductions of almost all amino acids in the liver and

Table 1-3. Metabolic Changes in Acute Pancreatitis

Increased	Decreased
Energy expenditure	Insulin response
Gluconeogenesis	Glutathione
Proteolysis	Vitamins A, C, and E
Urea turnover	Selenium
Lipolysis	Methionine
BCAA oxidation	Glutamine
Glutamine oxidation	

BCAA = branched-chain amino acid.

increased uptake of endogenous amino acids by the skeletal muscle mass, have been reported clinically and experimentally. The exact reason for this catabolism is not fully understood; however, the process of nitrogen loss and use closely resembles that which occurs during sepsis.

Gluconeogenesis increases, whereas glucose clearance and oxidation diminish, leading to glucose intolerance in 40–90% of cases. As a consequence, insulin can be required in up to 81% of patients. Reduced lipid clearance also has been documented in 12–15% of cases. A summary of metabolic changes that occur with acute pancreatitis is provided in Table 1-3.

Some studies indicate pancreatic damage occurs from activation of oxygen-derived free radicals in acute pancreatitis. Data suggest that glutathione and other sulfhydryl compounds are depleted and lipid peroxidation is increased in patients with acute and chronic pancreatitis. A recently published study assessed the contribution of oxidative stress in 320 patients with acute pancreatitis (90 severe) compared with 263 healthy controls. Statistically significant reductions of glutathione were noted at 24 and 48 hours from diagnosis in patients with both mild acute and severe acute pancreatitis compared with controls. The clinical significance of this level of depletion in antioxidant defenses has not been concretely established and questions linger regarding the amounts of antioxidants required for repletion.

Hypocalcemia is related to the severity of the disease and has been observed in 40–60% of patients with acute pancreatitis. Serum concentrations are maximally depressed during the first 3 days of the attack. The pathogenesis likely is multifactorial, involving saponification of calcium with free fatty acids, hypoalbuminemia, hypomagnesemia, increased calcitonin release, and decreased parathyroid hormone secretion. The first step for managing hypocalcemia should be to verify that the reduced serum calcium is not caused by hypoalbuminemia. If the ionized or corrected calcium is low (based on local laboratory standards), an attempt at correction should be made with calcium supplementation.

Nutritional Pathophysiology in Chronic Pancreatitis

Chronic pancreatitis may lead to maldigestion and malnutrition in some patients. This process is secondary to long-standing inflammation and fibrosis in the pancreas that destroys exocrine tissue, leading to inadequate delivery of

Dickerson RN, Vehe KL, Mullen JL, Fuerer ID. Resting energy expenditure in patients with pancreatitis. *Crit Care Med* 1991;19:484–90.

digestive enzymes to the duodenum in the prandial and postprandial period and in subsequent maldigestion. The development of exocrine insufficiency is not a universal feature of chronic pancreatitis and is seen only after long-standing disease. Some forms of chronic pancreatitis are more prone to exocrine insufficiency than others. Those with alcoholic, tropical, hereditary, and late-onset idiopathic chronic pancreatitis are particularly prone to exocrine as well as endocrine insufficiency, which still may take many years to develop. Those with early-onset idiopathic chronic pancreatitis, on the other hand, rarely develop either exocrine or endocrine insufficiency. In addition, tropical pancreatitis, a less common cause of pancreatitis found in southern India and other tropical areas, is associated with high-carbohydrate, low-protein, and very low-fat diets. The role of malnutrition in the etiology of tropical pancreatitis has been assessed in a few small studies and is still being defined. The fact remains that many patients affected by tropical pancreatitis maintain diets that are high in carbohydrates (e.g., white rice) and low in protein.

Patients with chronic pancreatitis caused by chronic ethanol ingestion are especially prone to malnutrition. They may be undernourished because of chronic alcohol abuse or poor oral intake resulting from the desire to avoid postprandial pain. In addition, these patients may have vitamin and mineral deficiencies resulting from malabsorption. They also may have steatorrhea or diabetes secondary to exocrine and endocrine pancreatic insufficiency. Steatorrhea does not appear to develop until lipase secretion has been diminished by at least 90%, a feature of long-standing and significant damage to the gland leading to malnutrition. Exogenous pancreatic enzyme supplementation-containing lipase usually is reserved for patients with fat malabsorption manifested as steatorrhea. Weight maintenance, symptomatic improvement of diarrhea, and/or a decrease in 72-hour fecal fat excretion are the goals of therapy.

Patients with chronic pancreatitis are relatively deficient in antioxidants, including vitamin C, vitamin E, selenium, and methionine, compared with healthy patients. Changes in glutathione metabolism, along with these antioxidant deficiencies, when paired with increased antioxidant demands, favor the formation of free radicals, which can lead to lipid peroxidation and cellular compromise. The deleterious effects of antioxidant deficiency in the presence of chronic pancreatitis may be one factor leading to an increase in inflammation and abdominal pain. Further investigation is required to confirm this theory in a large number of patients with chronic pancreatitis. A role for direct glutathione replacement or indirect replacement with *N*-acetylcysteine in chronic pancreatitis has not been clearly defined. There is a lack of controlled, clinical studies evaluating the therapeutic efficacy of antioxidant selenium or glutathione precursor supplementation in patients with acute pancreatitis. Therefore, controlled, clinical trials are needed to determine whether supplementation of antioxidants can alter the clinical course of acute pancreatitis as well as chronic pancreatitis.

Physiology of Exocrine Pancreatic Function

The release of digestive enzymes is mainly under the control of cholecystokinin and vagal cholinergic

stimulation, whereas vasoactive intestinal polypeptide influences bicarbonate secretion. The secretions of the exocrine pancreas total 1–2 L/day and the normal response to a meal contains twice the minimal enzyme requirement for normal digestion. It is believed that stimulation of pancreatic exocrine function in patients with acute pancreatitis releases large quantities of proteolytic enzymes, which results in autodigestion of the inflamed pancreas and peripancreatic tissues, causing deterioration in the patient's condition. Oral and nasogastric feedings increase pancreatic secretion by stimulating the cephalic and gastric phases. In addition, the presence of food in the duodenum elicits duodenopancreatic reflexes that result in stimulation of pancreatic exocrine secretions. These effects are not as pronounced when nutrients are delivered directly into the jejunum.

Maximal cholecystokinin release occurs in response to both amino acids and intact proteins. Complex solids lead to a more prolonged duration of pancreatic secretion than do homogenized solids, whereas liquids result in the shortest duration of stimulation. The exocrine pancreas also is stimulated by the presence of triglycerides and fatty acids in the stomach and duodenum. Maximal stimulation occurs with enteral long-chain triglycerides, whereas medium-chain triglycerides result in minimal stimulation. Thus, the use of medium-chain triglycerides in the diet of patients with acute and chronic pancreatitis may reduce stimulation of the exocrine pancreas and may be considered the first-line nutritional management strategy to minimize further pancreatic damage.

Different compositions of diets are associated with different amounts of pancreatic exocrine secretion. Studies have shown that diets containing fat are associated with more pancreatic amylase and lipase secretion in healthy patients compared to diets that contain predominately carbohydrate. This enzyme stimulation leads to the need to differentiate among diets based on fat content. When minimal pancreatic exocrine stimulation is desired, patients should receive fat-controlled diets (e.g., clear liquid, low-fat full liquid, low-fat regular, very low-fat regular, and no-fat regular). The amount of protein given (10–40% of the total calories) has not been associated with a significant difference in pancreatic enzyme secretion.

Nutritional Assessment in Acute Pancreatitis

Macronutrient Requirements in Severe Acute Pancreatitis

Protein

The catabolic state induced by the response to injury in acute pancreatitis leads to increased breakdown of endogenous protein and increased consumption of amino acids. Free amino acid concentrations decrease to 40% of normal. Concentrations of intracellular glutamine, the most abundant amino acid in skeletal muscle, decrease whereas glutamine use is increased. Levels of branched-chained amino acids (leucine, isoleucine, and valine) are slightly reduced, and concentrations of the aromatic amino acids are

markedly elevated. These changes in amino acid release and metabolism have led to the belief that branched-chain amino acid and glutamine-enriched amino acid solutions might be of particular benefit in patients with pancreatitis. Although this idea makes sense from a physiological standpoint, controlled, clinical trials are still needed to confirm this theory. In general, at least 1.5 g/kg/day of protein are required to improve nitrogen balance. However, it is difficult to improve nitrogen balance to the point of normalization in these patients, with even more protein likely indicated if pancreatitis is combined with sepsis or other complications. A nonprotein calorie-nitrogen ratio of 80–120:1 typically is required to ensure adequate protein use in patients with pancreatitis and severe to moderate nitrogen loss and catabolism. The ratio is derived as follows:

$$\text{NPC-N ratio} = \frac{\text{nonprotein calories (kcal/day)}}{\text{daily nitrogen intake (g)}}$$

$$\text{daily nitrogen intake (g)} = \frac{\text{daily protein intake (g)}}{6.25}$$

NPC-N = nonprotein calorie-nitrogen.

A randomized, controlled study in 28 patients with acute pancreatitis compared total parenteral nutrition (TPN) supplemented with glutamine (1.2 g/kg/day of aromatic amino acid plus 0.3 g/kg/day of glutamine) to standard TPN without glutamine (1.5 g/kg/day of aromatic amino acid). Acute pancreatitis was diagnosed using elevations in serum amylase concentrations and/or abdominal pain, and abdominal ultrasound or computed tomography of the abdomen. There was no stratification of patients based on pancreatitis severity. With a mean APACHE II score of 5.7 and 5.1 in the glutamine-supplemented and standard TPN groups, respectively, it appeared the majority of patients likely had mild acute pancreatitis. Treatment arms were relatively homogeneous with similar mean APACHE II scores, and calorie and protein intake in both groups. Glutamine supplementation with 0.3 g/kg/day significantly increased daily cost and reduced median number of TPN days compared with standard TPN (10 days vs. 16 days). Both groups experienced decreased CRP and lipase concentrations on days 7 and 14. Of interest, glutamine serum concentrations increased similarly in both groups. These data do not provide conclusive evidence of clear benefit of glutamine supplementation, with additional study required in patients with both mild and severe acute pancreatitis.

Carbohydrate

The metabolic response to injury results in the release of numerous counterregulatory hormones that lead to peripheral insulin resistance and hyperglycemia. A prior study documented that more than 80% of patients with pancreatitis who received TPN required 46–85 units/day of insulin. This glucose intolerance often creates the need to

titrate TPN to carbohydrate goals more slowly than in patients without intolerance. Intravenous carbohydrate goals should not exceed a glucose infusion rate of 5 mg/kg/minute, the maximal adult glucose oxidation rate, because of an increased likelihood of hepatic steatosis. In addition, high intravenous carbohydrate infusion rates can lead to excess carbon dioxide production, which can cause or worsen pulmonary compromise. Again, these complications occur when maximal glucose oxidation rates have been exceeded. In general, patients with pancreatitis are relatively glucose-intolerant; therefore, blood glucose concentrations exceeding 200 mg/dl and increased insulin requirements often precede carbohydrate intake reaching 5 mg/kg/minute. In fact, it may often be difficult to exceed 3 mg/kg/minute without signs of significant glucose intolerance. Clinicians must be mindful of these limitations in determining optimum intravenous carbohydrate intake. In comparison, enteral carbohydrates have a lesser effect on blood glucose control than equivalent quantities of parenteral carbohydrates.

A crossover study compared metabolic changes associated with 3-hour infusions of TPN to intragastric enteral nutrition (EN) in 10 healthy volunteers. Calorie and protein intake was equivalent with both forms of nutrition support. Energy expenditure, respiratory quotient, and glucose oxidation were similar in patients who were fed both parenterally and enterally over the 6-hour study period. However, blood glucose and insulin secretion were increased significantly during TPN infusion compared with EN. These data, along with anecdotal clinical experience, suggest that caution must be used with parenteral carbohydrate administration to minimize the likelihood of hyperglycemia. Tight blood glucose control is particularly difficult in patients with pancreatitis with or without a history of diabetes.

Caution must be used when adding exogenous insulin to TPN bags. In general, it is prudent to restrict insulin to less than 40 units/L with a maximum of 80 units/day. Exceeding these insulin amounts in TPN is fraught with potential for hypoglycemic episodes when patient's glucose intolerance improves. In patients with increased insulin requirements, it is important to first exclude carbohydrate intake excesses, then consider an exogenous insulin source outside of TPN. Continuous infusion insulin should be considered if sliding scale subcutaneous insulin has been inadequate.

Lipid

As previously discussed, strong evidence implicates enteral lipids as a culprit in pancreatic exocrine stimulation. Recent evidence suggests that enteral medium-chain triglycerides may be more appropriate in acute and chronic pancreatitis because of minimal pancreatic stimulation compared with long-chain triglycerides. A study performed in six healthy volunteers compared plasma pancreatic polypeptide secretion with oral long-chain triglycerides, medium-chain triglycerides, and saline. Ingestion of long-

Ockenga J, Borchert K, Rifai K, Manns PM, Bischoff SC. Effect of glutamine-enriched total parenteral nutrition in patients with acute pancreatitis. *Clin Nutr* 2002;21:409–16.

Vernet O, Christin L, Schutz Y, Danforth E, Jequier E. Enteral versus parenteral nutrition: comparison of energy metabolism in healthy subjects. *Am J Clin Nutr* 1986;43:194–209.

chain triglycerides induced significant increases in plasma pancreatic polypeptide secretion, with a lack of significant increases in pancreatic polypeptide noted after medium-chain triglycerides and saline ingestion. Cholecystokinin plays a major role in the intestinal phase of pancreatic polypeptide secretion; therefore, the decreased pancreatic polypeptide secretion after oral medium-chain triglycerides and saline administration is thought to have resulted from a decreased release of cholecystokinin. These results observed in healthy patients have yet to be confirmed in comparative studies in patients with pancreatitis.

Although years of clinical experience suggest its safety, the use of intravenous lipid emulsion in patients with acute pancreatitis remains controversial. The confusion is related to the known association between hypertriglyceridemia and pancreatitis. High serum triglyceride concentrations can both cause and result from pancreatitis. In fact, anything that causes pancreatitis can increase triglyceride concentrations. Therefore, the decision about whether to give intravenous lipids to a patient with pancreatitis should be based on the cause of the pancreatitis, if known, and the patient's current serum triglyceride concentration. Meeting daily lipid requirements in patients with preexisting hypertriglyceridemia is particularly difficult. An example is a patient with profound hypertriglyceridemia (more than 1000 mg/dl), as seen with protease inhibitor therapy. In these instances, the nutrition support plan must be modified to provide low to no lipids while monitoring triglyceride concentrations every 5–7 days for a decline to less than 400 mg/dl.

The notion that parenteral lipids are safe in patients with pancreatitis is based on the theory of minimal exocrine pancreatic stimulation. This theory has been confirmed in studies involving small numbers of patients. One study assessed the pancreatic exocrine stimulation and pancreatic fistula output occurring after parenteral lipid administration in three patients with pancreatic fistulae. All three patients received TPN consisting of alternating periods of isocaloric, isovolumetric, and isonitrogenous solutions with and without lipids. During the periods when lipids were infused, two patients received 1000 ml of 10% soybean oil emulsion, and the other received 500 ml of 10% soybean oil emulsion. Fistula volume, amylase, and lipase concentrations were evaluated. Because patients were studied over varying time periods, an analysis of variance tested for interaction between the effect of the time period and the effects of the intravenous solutions on outcomes. Overall, the patients experienced either no change in fistula output, amylase, and lipase concentrations or significant declines in fistula output, amylase, and lipase concentrations during lipid administration. Despite the small number of patients involved in the case series, it provides some evidence supporting the lack of deleterious increases in pancreatic exocrine stimulation with parenteral lipid administration.

Based on the previous study and anecdotal experience, the American Society for Parenteral and Enteral Nutrition

guidelines conclude that parenteral lipids are safe in patients with pancreatitis with triglyceride concentrations less than 400 mg/dl. Routine monitoring of triglyceride concentrations is recommended in all patients with pancreatitis receiving parenteral lipids, even patients with previously normal triglyceride concentrations. Up to 30% of nonprotein calories can be given routinely as lipids without difficulty, provided that low triglyceride concentrations are maintained.

Role of Nutrition Support Therapy in Severe Acute and Chronic Pancreatitis

Role of Nutrition Support in Mild Acute Pancreatitis

Patients with mild acute pancreatitis are not usually malnourished and are able to eat normally within 5–7 days of disease onset, so nutritional support is unnecessary. In general, patients with mild acute pancreatitis without signs of malnutrition may be treated with supportive care, including intravenous fluids and pain control, for 3 days. After avoidance of oral nutrition for 72 hours, a decision must be made regarding the status of the patient and what nutrition support strategy is most suitable. Many clinicians choose to initiate a clear liquid or low-fat full liquid, transitioning to a low-fat, very low-fat, or no-fat regular diet in patients with mild acute pancreatitis with clinical success demonstrated using this strategy.

Although mild acute pancreatitis attacks often resolve promptly, the cumulative effects of repeated attacks, chronic relapsing pancreatitis, can lead to malnutrition. The duration that patients cannot receive oral nutrition depends on the degree of malnutrition and differs for each patient. In malnourished patients, it is important to gain a historical perspective of previous responses to EN support regimens. The goal is to minimize pancreatic exocrine stimulation by challenging patients with the conservative fat-controlled enteral diets if tolerated and advancing enteral fat content if possible. Total parenteral nutrition should be reserved as a last resort for profoundly malnourished patients who cannot tolerate fat-controlled diets.

Role of Nutrition Support in Severe Acute Pancreatitis

The subset of patients with severe acute pancreatitis is at risk for a protracted disease course, typically with an inability to achieve an oral diet by day 7. Nutritional depletion impairs host defenses, immune competence, and resistance to nosocomial infections, possibly complicating the course of severe pancreatitis. As previously discussed, such patients may have preexisting protein-calorie malnutrition and micronutrient deficiencies. Patients who

De Jong AJ, Hopman WP, Jansen JB, Lamers CB. Effect of medium-chain triglycerides and long-chain triglycerides on plasma pancreatic polypeptide secretion in man. *Regul Pept* 1985;11:77–81.

Grundfest S, Steiger E, Selinkoff P, Fletcher J. The effect of intravenous fat emulsions in patients with pancreatic fistula. *JPEN J Parenter Enteral Nutr* 1980;4:27–31.

Table 1-4. Adult Substrate Requirements in Acute Pancreatitis

Total calories	25–35 kcal/kg/day
Carbohydrates	Less than 5 mg/kg/minute plus exogenous insulin
Fat	Less than 1.5 g/kg/day (monitor triglyceride concentrations)
Protein	1.5–2 g/kg/day
Vitamins, trace elements	Vitamins A, C, and E and selenium

are diagnosed with severe acute pancreatitis require appropriate calories and nitrogen to prevent further nutritional and clinical compromise. Table 1-4 lists substrate requirements for patients with acute pancreatitis. Limited studies have suggested that daily administration of trace elements and vitamin antioxidants should include 600 mcg of selenium, 9000 IU of vitamin A, 500 mg of vitamin C, and 270 IU of vitamin E. These trace elements and vitamin antioxidants can be administered within the parenteral nutrition solution, orally, or through a feeding tube. Trace element and vitamin supplementation has been successful in restoring endogenous serum concentrations to the normal range; however, it has yet to be associated with improved clinical outcomes in patients with pancreatitis.

Autodigestion by activation of pancreatic enzymes is the primary theory for the pathogenesis of acute pancreatitis. On the basis of this theory, nutritional management of severe acute pancreatitis first focuses on avoiding pancreatic stimulation. As previously discussed, pancreatic exocrine secretion is stimulated by both intragastric and intraduodenal stimuli. Studies performed in healthy individuals and patients with pancreatitis suggest that delivery of an elemental formula distal to the ligament of Treitz minimizes pancreatic secretion and bypasses the physiological gastropancreatic and duodenopancreatic secretory mechanisms. Many commercial feeding tubes are relatively short in length and terminate at the level of the ligament of Treitz or the proximal jejunum, making distal jejunal feedings somewhat difficult. The most common and successful technique used in clinical research for feeding tube placement past the ligament of Treitz was endoscopic nasal placement into the second loop of jejunum. In some instances, the placement of tubes through the pylorus, the most crucial step of the procedure, was performed by radiologists. The correct placement also may be confirmed by radiograph. The following feeding tubes have been successfully positioned past the ligament of Treitz: Angiomed duodenal set (150 cm) and Flocare (125 cm). Discussion continues regarding the ideal enteral formula and route of enteral delivery. The ideal placement of a feeding tube is discussed in more detail in the Optimal EN Feeding Tube Placement section.

The best route for nutritional support in severe acute pancreatitis, enteral or parenteral, also remains debatable. Total parenteral nutrition traditionally has been recommended in this setting because of evidence of minimal pancreatic stimulation. However, recent studies identified

EN strategies associated with good overall patient outcomes compared to TPN. These data supporting EN are changing the practice environment, particularly in teaching hospitals. In fact, these data have led to EN becoming the nutrition support modality of choice for patients with pancreatitis because of the minimal associated metabolic and infectious complications compared with TPN. The role of EN in managing severe acute pancreatitis is discussed in more detail in the Indications for EN section.

Pancreatic enzyme supplementation, which has been beneficial in chronic pancreatitis, has not demonstrated a benefit in severe acute pancreatitis. Therefore, exogenous enzyme supplementation has no role in severe acute pancreatitis management.

Role of Nutrition Support in Chronic Pancreatitis

Pain is the most profound characteristic of chronic pancreatitis. The persistent prandial and postprandial pain associated with chronic pancreatitis may lead to decreased oral intake and subsequent weight loss in patients wishing to avoid episodes of epigastric discomfort. When weight loss is evident in patients with chronic pancreatitis, a high total caloric intake of 30–35 kcal/kg/day is likely necessary. In general, an oral diet of 50 g/day of fat is well tolerated, especially one rich in vegetable fat. Enteral formulations with medium-chain triglycerides may be used to increase fat absorption and minimize pancreatic stimulation. In addition, elemental and semielemental enteral formulas are believed to have similar benefits in chronic pancreatitis.

Indications for EN

Demonstrated benefits of EN in other diseases led to the evaluation of the enteral route in patients with acute pancreatitis. Studies in patients with severe acute pancreatitis demonstrated that EN was well tolerated. Patients who received enteral feedings experienced significantly fewer total complications and had a lower risk of developing septic complications than those receiving TPN. A prospective, comparative, outcomes study assessed acute phase response and pancreatitis disease severity in 34 patients with mild and severe acute pancreatitis receiving TPN (18 patients) or EN (16 patients). Glasgow criteria of three or more was required for a diagnosis of severe acute pancreatitis. Clinical outcome measures of systemic inflammatory response syndrome, sepsis, multiple organ failure, and mortality were all improved in patients who were fed enterally. In addition, 82% of patients who were fed enterally had systemic inflammatory response syndrome resolution compared to 17% in patients fed parenterally. Another study of patients with mild acute pancreatitis reported a more rapid normalization of physiological disturbances in patients who received EN compared with TPN. This study supported the safety of early enteral feeding in mild acute pancreatitis.

A meta-analysis involving six randomized, clinical trials comparing EN and TPN in 263 total patients with mild and severe acute pancreatitis showed a significantly lower relative risk of infection (e.g., pneumonia, abdominal

Windsor AJ, Kanwar S, Li AK, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut* 1998;42:431–5.

abscess, pancreatic abscess, wound infections, and blood stream infections) in patients receiving EN compared to patients receiving TPN (relative risk = 0.45; 95% confidence interval = 0.26–0.78; $p=0.004$). The test result for heterogeneity between the studies was not significant ($p=0.59$). In addition, the requirement for surgery was significantly lower in patients receiving EN (relative risk = 0.48; 95% confidence interval = 0.23–0.99; $p=0.05$). Again, the test result for heterogeneity between studies was not significant ($p=0.89$). Limitations of this meta-analysis included the use of studies that reported the provision of EN through feeding tubes in the small bowel without documentation of the exact location of all tubes. In addition, these small, nonblinded studies did not use a consistent stratification method for differentiating mild and severe acute pancreatitis cases, creating some difficulty in maintaining homogeneity among the studies; however, this inconsistency was taken under consideration during the meta-analysis.

After compiling data from these studies along with clinical experience, it appears that EN does not have a deleterious effect on markers of inflammation and clinical outcomes. In fact, a beneficial decrease in markers of inflammation is likely possible, with more study needed to confirm this notion. The data associating TPN with increased infectious complications compared with EN are quite compelling as well. Based on these findings, EN can be considered first-line nutritional management in patients with severe acute pancreatitis.

Selecting EN Formulas

Selecting EN Formulas in Acute Pancreatitis

Another pivotal issue regarding EN in the setting of acute pancreatitis is the choice of the ideal formula to facilitate positive outcomes. The available formulas can be classified according to three general composition considerations: elemental or semielemental (e.g., short-chain peptides), polymeric formulas (intact protein composition), and the immune-enhancing formulas.

At this time, the majority of studies assessing nasojejunal feedings for acute pancreatitis use the elemental or semielemental formulas, on the belief that they are the least likely to stimulate the pancreas. Elemental and semielemental formulas contain unbound amino acids and short-chain peptides, respectively, along with relatively small amounts of long-chain fatty acids. Therefore, substantial pancreatic stimulation should not be needed for product absorption. This theory still requires comparative testing with standard EN formulas in controlled trials involving patients with acute pancreatitis. Conversely, EN composed of oligopeptides with limitations on the amount of long-chain triglycerides has a proven association with minimal exocrine pancreas stimulation in patients with chronic pancreatitis. Clinical and economic outcomes studies are needed to confirm an advantage that justifies the increased cost of medium-chain triglyceride-containing formulas compared to long-chain triglycerides.

Immune-enhancing diets with glutamine and arginine have been beneficial in other patient populations, including burn and wound care patients. These EN formulas are the latest potential strategy in patients with acute and chronic pancreatitis. A nonblinded study performed over a 10-day period compared the changes in immunological parameters in 16 patients with mild and severe acute pancreatitis who received early jejunal nutrition with a glutamine-rich, fiber-containing formula (Stresson Multi Fibre, nine patients) compared with a nonimmune-enhanced standard formula (Nutrison Fibre, seven patients). These immunological parameters, particularly CRP, are thought to have a close connection with the process and severity of pancreatitis. There was a significant reduction in intensive care unit length of stay noted with the glutamine-rich diet, a median of 8.6 days (range of 0 to 28 days) compared to 34.8 days (range of 6 to 151 days) with standard EN. Detailed statistical analysis of these outcome data was not provided. In addition, there was a noted increase in prealbumin; fibrinogen; and immunoglobulins A, M, and E, as well as a decrease in CRP in the patients who received glutamine-rich diets. However, none of the changes in immunological parameters reached statistical significance through the 10-day study period. The lack of statistical significance may be secondary to the small sample size of the study. Another limitation was the observational approach to evaluation of outcomes. Despite these limitations, this study suggests that there may be a role for immune-enhancing formulas; however, that role has yet to be clearly defined.

At present, elemental and semielemental enteral formulations appear to be the least problematic and, because most new research involving EN support uses these formulas, many clinicians consider them a prudent first option compared with standard polymeric and immune-enhancing formulas. However, there is a need for large randomized studies to compare these formulations in patients with acute pancreatitis.

Selecting EN Formulas in Chronic Pancreatitis

A recent study assessed postprandial pain amelioration in outpatients with chronic pancreatitis receiving oral feedings containing medium-chain triglycerides and hydrolyzed proteins (Peptamen). This study included eight patients who experienced pain at least 3 times/week over 3 or more weeks before enrollment and in whom conventional pain management therapies failed, including high-dose pancreatic enzymes, antioxidants, low-fat diet, and celiac plexus nerve blocks. Postprandial pain was significantly reduced in six (75%) patients. This reduction in pain resulted in either decreased narcotic requirements or the ability to discontinue narcotics altogether. The improvement in pain management was secondary to decreases in cholecystokinin release. As a result, researchers concluded that an enteral supplement-containing medium-chain triglycerides and hydrolyzed proteins minimally increases plasma cholecystokinin concentrations and may be useful in

Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. *BMJ* 2004;328:1407–12.

Hallay J, Kovacs G, Szatmari K, et al. Early jejunal nutrition and changes in the immunological parameters of patients with acute pancreatitis. *Hepatology* 2001;48:1488–92.

treating postprandial pain in patients with chronic pancreatitis. These results provide support for oral formulas containing medium-chain triglycerides and hydrolyzed proteins to be considered in the setting of chronic pancreatitis.

Optimal EN Feeding Tube Placement

The decision to initiate EN support also includes the choice of feeding tube placement. As previously discussed, the point at which EN is introduced into the gastrointestinal tract is an important factor in bowel rest, ensuring that minimal pancreatic exocrine stimulation occurs. There are three main categories of enteral access available to patients with acute pancreatitis: nasal (nasogastric/nasoduodenal/nasojejunal tubes), percutaneous (percutaneous gastrostomy/jejunostomy tubes), and surgical (surgical gastrostomy/jejunostomy tubes). Nasal placement of feeding tubes is the most straightforward, least invasive, and least expensive strategy of the three options. Therefore, this short-term feeding approach is the most commonly used. Percutaneous and surgical feeding tube placements are intermediate and long-term feeding strategies, respectively.

Several experimental and clinical trials have shown that delivery of nutrients into the jejunum does not increase pancreatic secretion and is well tolerated. More specifically, administering lipids into the duodenum is a strong stimulatory factor for pancreatic exocrine secretion, whereas jejunal delivery of the same amount of lipids causes minimal pancreatic reaction.

A study compared outcomes in 60 patients with mild and severe acute pancreatitis with and without peritonitis who received early jejunal feedings (30 patients) of either a full-strength standard polymeric formula (Nutrison Standard) or oligopeptide-based formula (Nutrison Pepti) to a control group who received intravenous fluids only until reintroduction of regular diet (30 patients). An APACHE II score of 6 or more was used; therefore, patients with mild acute pancreatitis were included. There were significantly fewer unresolved peritonitis cases with jejunal feedings (3.3%) compared with the control group (26.7%; $p < 0.05$), and mortality rates were lower in patients receiving jejunal feedings (3.3%) than in the control group (23%; $p < 0.05$). Total nutritional daily intake after surgery was higher in the jejunal feeding group (1294.6 kcal) than in the control group (472.8 kcal; $p < 0.0001$). Of interest, both oligopeptide-based and whole protein-based formulas were used with demonstrated benefits compared with intravenous fluids alone. A limitation of the study was lack of documentation of exact feeding tube position in the jejunum. The Flocare nasojejunal tube (125 cm in length) was used, making feeding past the ligament of Treitz feasible. Despite this limitation, these data support the need to initiate EN as early as possible. These data also fuel the argument that jejunal feeding tube placement is an even more important factor to ensure minimal pancreatic exocrine stimulation than fat (medium-chain triglycerides vs. long-chain triglycerides) and/or protein (polymeric vs. elemental) content of EN formulas.

A randomized, comparative, outcomes study in 53 patients with mild and severe acute pancreatitis compared jejunal elemental feedings (26 patients) with TPN (27 patients). Researchers enrolled all patients admitted with acute abdominal pain and a 3-fold elevation of serum amylase and lipase, as well as a primary diagnosis of acute pancreatitis who required nutrition support after a 48-hour bowel rest period. The average hospital length of stay was 4 days shorter for patients fed enterally (14.2 days) than for patients who received TPN (18.4 days); however, statistical significance was not met. Because of the conservative EN titration protocol used in the study, patients who were fed enterally received significantly fewer nutrients (average 49% of estimated calories and 42% of protein requirements) than patients fed parenterally (average 85% estimated calories and protein requirements) ($p < 0.005$). Median blood glucose concentrations were significantly lower (138 mg/dl) in patients receiving EN than in patients receiving TPN (180 mg/dl; $p = 0.03$). In addition, hyperglycemia requiring insulin therapy was statistically more common in patients receiving TPN than EN (four vs. 14, respectively; $p = 0.03$). Catheter-related infections requiring intravenous line removal and antibiotic treatment were less common in the EN group compared with TPN (one vs. nine, respectively; $p = 0.01$). There also was a significantly lower average cost for nutritional support in the EN group (\$394/patient) than in the TPN group (\$2,756/patient; $p = 0.0004$). This difference in expenditure also extended to significantly lower daily costs for EN (\$23.30/day) compared with TPN (\$222/day). There was no distinction made in the study regarding whether costs data were based on hospital costs or patient charges. This distinction in cost derivation is necessary before these dollar amounts can be extrapolated to other health care institutions. Researchers also failed to distinguish which particular elemental formula was used during the study. Despite these limitations and the hypocaloric nature of the jejunal feedings, positive results were observed, similar to other EN studies in this setting. These results confirmed that hypocaloric jejunal feedings with an elemental formula are safer, less expensive, and allow for faster disease resolution compared with TPN; therefore, they may be considered first-line management of severe acute pancreatitis.

A similar two-phase outcomes study compared complications in 89 patients with mild and severe acute pancreatitis receiving either early (within 24–48 hours after symptom onset) elemental jejunal feedings (Servimed OPD) (41 patients) or TPN (48 patients) during Phase I. The feeding tube placement was confirmed to be in the second loop of the jejunum. Phase II of the study included the concomitant administration of imipenem-cilastatin for bacterial prophylaxis in 92 patients receiving jejunal feeding with evidence of pancreatic necrosis on abdominal computed tomography. Similar to previous studies involving EN support in patients with severe acute pancreatitis, goal EN rates were not achieved because of tube feeding intolerance associated with high-volume intake. Despite an inability to advance EN to goal, the

Pupelis F, Selga G, Austrums E, Kaminski A. Jejunal feeding, even when instituted late, improves outcomes in patients with severe pancreatitis and peritonitis. *Nutrition* 2001;17:91–4.

incidence of septic complications (i.e., infected pancreatic necrosis or late abscess) was lower in patients fed enterally (12%) than in patients fed parenterally (27%). However, this difference was not statistically significant ($p=0.08$). During Phase II of the study, the incidence of septic complications was lower in patients fed enterally receiving bacterial prophylaxis (13%) than in patients fed parenterally (27%; $p=0.04$). Conversely, there was no difference in rates of septic complications observed in patients receiving EN with or without bacterial prophylaxis (12% vs. 13%, respectively; $p=NS$). These results further confirm the safety of early jejunal feedings compared to TPN. In addition, prophylactic antibiotic therapy appeared to have a role in combination with jejunal feedings in patients with pancreatic necrosis. However, an addition of a fourth arm to this study with patients fed parenterally receiving antibiotic therapy would have helped differentiate the impact of antibiotic therapy from the influence of EN support.

Oxidative stress has been considered as a theoretical cause for tissue damage in mild and severe acute pancreatitis. A prospective, randomized study compared the effect of jejunally administered standard polymeric enteral formula (Nutrison and Polycal) on markers of oxidative stress (eight patients) with TPN (nine patients) in 17 patients with mild or severe acute pancreatitis. A weighted, nasojejunal, dual-lumen tube (Medicina) was inserted blindly, with radiographic confirmation of jejunal placement. The specific location of the tube in the jejunum was not indicated. A low APACHE II score cutoff of 6 or more was used to classify severe acute pancreatitis; therefore, mild acute cases were enrolled. The time to return of normal bowel function (2 vs. 3 days, respectively; $p=0.01$), the time to transition to a full oral diet (2 vs. 3 days, respectively; $p=0.02$), and hospital length of stay (7 vs. 10 days, respectively; $p<0.05$) were statistically shorter in patients receiving jejunal EN compared with TPN. There was no difference in either treatment arm over the 7-day study period in the following measures of oxidative stress: thiobarbituric acid-reactive substances ($p=0.49$) and plasma glutamine concentrations ($p=0.05$). This study found no antioxidant effect with the EN regimen. More important, no deleterious effect on oxidative stress or glutamine metabolism was related to immediate EN in mild and severe acute pancreatitis.

A retrospective, observational study compared outcomes in 63 patients who underwent surgery because of deterioration of severe acute pancreatitis and who had received either standard polymeric jejunal feedings (PreNutrison) (33 patients) or standard therapy (i.e., dextrose-containing intravenous fluids, colloids, and antibiotic drugs) alone (30 patients). At least 300 ml/day of a standard enteral formula was provided in the jejunal feeding arm. The total nutritional daily intake was higher in the jejunal feeding group (1203.8 ± 391.8 kcal) compared with the standard therapy group (455.1 ± 151.6 kcal; $p<0.0001$). An unspecified oral liquid diet was started after a mean of 10.5 days and 9.1 days in the jejunal feeding and

standard therapy groups, respectively. Significantly lower rates of late (i.e., more than 3 days after admission) pulmonary complications (e.g., pleural effusion, atelectasis, and pneumonia) (15.2% vs. 43.3%; $p<0.05$), late renal insufficiency (0% vs. 26.7%; $p<0.05$), wound- and catheter-related septic complications (9.1% vs. 30%; $p<0.05$), and mortality (6.1% vs. 26.7%; $p<0.05$) were reported in patients who received jejunal feedings compared with the standard therapy group. The retrospective nature of this study is a limitation, particularly considering the potential for selection bias for patients to receive either jejunal feedings or standard therapy. Criteria for inclusion into either treatment arm were not provided. Despite these limitations, the outcome improvements in patients receiving jejunal feedings are similar to previously published data, with the exception of the significant improvement in mortality, which had not been reported in prior studies. These positive outcomes appear to be attributable to jejunal feedings, creating an argument that standard polymeric formulas do not adversely impact pancreatic exocrine stimulation in the setting of jejunal administration. The potential for mortality benefit must be confirmed in a large prospective, randomized fashion.

Indications for Parenteral Nutrition

Studies also have addressed the effects of various nutrients administered parenterally on pancreatic exocrine secretion. Two studies showed that parenteral infusion of glucose did not stimulate pancreatic exocrine secretion. In addition, a series of small well-controlled studies performed in healthy volunteers demonstrated that parenteral infusion of lipid does not stimulate pancreatic exocrine secretion. The consensus of these data is that mixed substrate infusion (carbohydrate, protein, and fat) does not stimulate exocrine pancreatic secretion.

Data also have shown that intravenous lipids are not detrimental to patients with acute pancreatitis in the absence of hypertriglyceridemia. However, as previously discussed, hypertriglyceridemia is a potential risk factor for pancreatitis; therefore, weekly monitoring of serum triglyceride concentrations is recommended during intravenous lipid administration in patients with pancreatitis. Serum triglyceride concentrations above 1000 mg/dl may precipitate attacks of acute pancreatitis. However, triglyceride concentrations of 500–1000 mg/dl also may induce acute pancreatitis; therefore, intravenous lipids are not recommended in these patients with serum triglyceride concentrations in this range.

Few studies evaluate the concept of immunonutrients in severe acute pancreatitis in humans. Researchers have shown that glutamine-supplemented TPN might improve lymphocyte activity and reduce proinflammatory cytokine release in patients with severe acute pancreatitis compared with standard TPN. However, there are not enough data supporting this strategy to make it a first-line option.

Many studies have elucidated the metabolic and infectious complications associated with TPN in the setting

Olah A, Pardavi G, Belagyi T, Nagy A, Issekutz A, Mohamed GE. Early nasojejunal feeding in acute pancreatitis is associated with a lower complication rate. *Nutrition* 2002;18:259–62.

Austrums E, Pupelis G, Snippe K. Postoperative enteral stimulation by gut feeding improves outcomes in severe acute pancreatitis. *Nutrition* 2003;19:487–91.

of acute pancreatitis and other patient populations. A recent study in 27 patients with severe acute pancreatitis compared the effect of nasojejunal administration of an isotonic, polymeric formula-containing fiber (13 patients) with TPN (14 patients) on markers of inflammatory response. Enteral nutrition had no beneficial effect on markers of inflammatory response, including CRP ($p=0.62$), interleukin-6 ($p=0.28$), soluble tumor necrosis factor receptor inhibitors ($p=0.53$), or on organ dysfunction ($p=0.52$) compared to TPN. The lack of a decrease in inflammatory response with EN may be explained by the fact that only 21% of daily caloric requirements were met because of a conservative EN titration protocol. The findings of this study seem to suggest that “minimal” amounts of EN do not modify the inflammatory response in acute pancreatitis. In addition, the 4-day study period in which inflammatory markers were measured may not be sufficient to obtain a true measure of EN effects on these markers of inflammation. Previous studies of immunonutrition in patients with cancer support that at least 10 days of EN are necessary to observe this effect.

Pancreatic rest and avoidance of exocrine stimulation, by preventing oral nutrient intake in conjunction with nutritional support by the parenteral route, has been the cornerstone of treatment of acute pancreatitis to promote early recovery. However, in light of recent evidence confirming the safety and efficacy of EN, the role of TPN has shifted from first-line nutritional management of most severe acute pancreatitis episodes to limited nutritional management of severe acute pancreatitis complicated by fistulae, necrosis, or prolonged ileus. Pseudocysts, intestinal and pancreatic fistulae, pancreatic abscesses, and pancreatic ascites are known complications of acute pancreatitis, occurring in up to 25% of patients. These complications are relative contraindications for EN. Total parenteral nutrition is recommended in these patients, in conjunction with appropriate treatment for the complications.

Role of Exogenous Pancreatic Enzyme Supplementation in Chronic Pancreatitis

Pancreatic enzyme supplementation has two roles in patients with chronic pancreatitis. The first is to treat malabsorption caused by pancreatic insufficiency. The most limiting aspect of pancreatic enzyme supplementation is lipase activity. In general, a low-fat diet (less than 20 g of fat), in conjunction with pancreatic enzyme supplementation with meals and snacks, is sufficient.

The other role of pancreatic enzymes is pain management for patients with chronic pancreatitis. As previously discussed, oral administration of high doses of pancreatic enzymes (more than 30,000 IU/meal) may decrease pain by minimizing release of cholecystokinin.

Large randomized, controlled trials assessing outcomes (e.g., improvement in malabsorption, pain, or weight gain) in patients with chronic pancreatitis receiving exogenous pancreatic enzymes are lacking. However, there are small randomized studies evaluating this modality of therapy along with growing clinical and anecdotal experience.

Pancreatic enzyme supplements are highly variable in enzyme activity with lipase contents ranging anywhere from 4000 IU/dose to 20,000 IU/dose (Table 1-5 contains for a

Table 1-5. Pancreatic Enzyme Products Available in the United States

Dosage Form	Enzyme Product	Units of Lipase/Dose
Powder	Viokase powder	16,800 per ¼ teaspoon
Nonenteric-coated	Viokase 8, 16 tablets	8000, 16,000
	Ku-Zyme HP capsules	8000
	Pancrelipase tablets	8000, 16,000
	Panokase tablets	8000
	Plaretase tablets	8000
	Generic	8000
Enteric-coated	Creon 5, 10, 20 capsules	5000, 10,000, 20,000
	Lipram 4500 capsules	4500
	Lipram CR5, CR20 capsules	5000, 20,000
	Lipram PN10, PN16, PN20 capsules	10,000, 16,000, 20,000
	Lipram UL12, UL18, UL20 capsules	12,000, 18,000, 20,000
	Ultrase MT12, MT18, MT20 capsules	12,000, 18,000, 20,000
	Pancrease MT4, MT10, MT16, MT20 capsules	4000, 10,000, 16,000, 20,000

more detailed description). In April 2004, the Food and Drug Administration announced that all exocrine pancreatic insufficiency drug products are new drugs and subject to conditions for continued marketing. In addition, the Food and Drug Administration made these products available by prescription only. Manufacturers have until 2008 to submit new drug applications and receive Food and Drug Administration approval to continue marketing their products. This process will ensure the availability of additional bioequivalence data. At this time, the Food and Drug Administration does not have sufficient data to determine therapeutic equivalence of these products; therefore, the Food and Drug Administration currently does not recommend product substitution.

Overall, a minimal lipase dose of 28,000 IU/meal is required for maximal enzyme activity. Therefore, pancreatic enzymes products should be initiated at a dose of 28,000–30,000 IU with meals and titrated based on response. The effectiveness of enzyme supplementation typically is gauged by clinical parameters, including improvement in stool consistency, loss of visible fat in the stool, and gain in weight. Performing a 72-hour fecal fat analysis before and during therapy to prove effectiveness is rarely needed but can be considered in situations in which enzyme supplementation fails to yield clinical response as expected. The enzyme supplementation products marketed in the United States are available in several different dosage forms, including tablets, powders, and enteric-coated capsules. Nonenteric-coated tablets and powders are destroyed by gastric acid and require coadministration of drugs to decrease gastric acid secretion (e.g., histamine-2 receptor antagonists or proton-pump inhibitors). This alteration in gastric acidity is not usually required when enteric-coated or microencapsulated preparations are used. Because of the variability in lipase content of these

products, the quantity of tablets, capsules, or powder will vary.

Oral tablets and capsules increase in size as lipase content increases, potentially causing swallowing difficulties for some patients. In addition, these products may lead to small-bore feeding tube obstructions when administered by this route. This problem may be remedied by dissolving the obstruction with 5–10 ml of sodium bicarbonate administered into the feeding tube with agitation until the obstruction clears. As a general rule, microencapsulated products should remain intact. Opening the microencapsulated capsules or crushing the microspheres will decrease the products' absorption in the duodenum and negate any protection from gastric acid. These distinguishing characteristics among the pancreatic enzyme products must be considered when making formulary decisions for a given institution or making treatment decisions for an individual patient.

An ideal pancreatic enzyme preparation should contain a high concentration of lipase to maximize fat digestion and a high concentration of proteases to maximize protein absorption, reduce pain, and resist gastric acidity. In addition, the ideal preparation will empty from the stomach with food in synchrony and release enzymes immediately on entering the duodenum. Such an ideal product does not exist.

Therapeutic Goals and Desired Outcomes in Acute and Chronic Pancreatitis

No matter which nutrition management strategy is used, initiating an oral diet as soon as possible is the overall goal that remains constant for patients with mild acute, severe acute, and chronic pancreatitis. This goal is easily met in the majority of patients with mild acute pancreatitis. These patients will likely tolerate oral diets within 3–5 days of symptom onset. Conversely, patients with severe acute pancreatitis will likely require either EN or TPN support until oral diets are tolerated. In these patients, therapeutic goals are to counteract catabolism, abate pancreatic inflammation by decreasing exocrine stimulation, and to manage metabolic disturbances that may be present. The hallmark of chronic pancreatitis is recurrent postprandial epigastric pain, which may indirectly lead to malnutrition secondary to decreased oral intake. Therefore, therapeutic goals in these patients involve pain management and repletion of nutritional deficits. Exogenous pancreatic enzymes and EN with medium-chain triglycerides and hydrolyzed proteins have a role in reducing pain in these patients with chronic pancreatitis.

Conclusion

Nutritional management of acute and chronic pancreatitis begins by classifying the severity of pancreatitis. After the severity of pancreatitis has been determined, a nutritional

assessment may then be initiated. Recent literature more clearly defines the role of EN and TPN in the setting of acute, chronic, and necrotizing pancreatitis. The comparisons of various EN formulas, feeding tube placements, and TPN strategies are ongoing to identify regimens that lead to positive patient outcomes.

Annotated Bibliography

1. ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr* 2002;26(1 suppl):1SA–138SA.

The clinical guidelines task force of the American Society for Parenteral and Enteral Nutrition compiled an excellent reference for evidence-based nutrition practice. The recommendations are specific, and primary literature citations are provided. Recommendations for nutrition support of adults and children with pancreatitis and many other diseases are included. The expert panel's recommendations regarding the nutritional management of patients with pancreatitis include the need to instruct clinicians to perform nutritional screenings and assessments and treatment plans for all patients with pancreatitis. Recommendations differentiate the role of nutrition support in patients with mild acute, severe acute, necrotizing, and chronic pancreatitis. In addition, the recommendation to initiate enteral nutrition (EN) as first-line management over parenteral nutrition in most patients with severe acute pancreatitis is provided. The indications for parenteral nutrition are identified, and the role of intravenous lipids is addressed definitively.

2. Kahl S, Zimmermann S, Malfertheiner P. Acute pancreatitis: treatment strategies. *Dig Dis* 2003;21:30–7.

This article provides a comprehensive review, including the most recent literature published in the realm of nutrition support in acute pancreatitis. A description of outcomes from selected randomized trials comparing EN to total parenteral nutrition (TPN) is provided, spanning the past 5 years of research. Other therapeutic approaches to managing patients with acute pancreatitis are included in addition to nutrition support strategies. Areas of clinical interest include managing dehydration, pain, hyperglycemia, and electrolyte abnormalities. The literature supporting bacterial prophylaxis in necrotizing pancreatitis also is discussed. An evidence-based review of bacterial etiologies of infections in pancreatic necrosis and comparative data of antibiotic coverage are evaluated. In addition, data concerning experimental drug and nutritional strategies are described, identifying areas of interest for future clinical research.

3. Shea JC, Bishop MD, Parker EM, Gelrod A, Freedman SD. An enteral therapy containing medium chain triglycerides and hydrolyzed peptides reduces postprandial pain associated with chronic pancreatitis. *Pancreatology* 2003;3:36–40.

This small controlled, prospective study defined a role for EN formulations containing medium-chain triglycerides and hydrolyzed proteins in reducing cholecystokinin release and pain scores in patients with chronic pancreatitis. The study is of particular interest because of the potential impact that EN may have in patients with pain refractory to conventional therapy, including analgesics and pancreatic enzymes. The enteral formula used in the study was administered orally to patients with chronic pancreatitis who suffered from

refractory postprandial pain at least 3 times/week for more than 2 weeks before study enrollment. A visual analog scale was used to assess pain with a range of 0 to 10. All patients had been treated previously with other pain management modalities, including opiate analgesics, without adequate pain relief. On administration of EN, postprandial pain was significantly reduced in the majority of patients. The median improvement in pain scores for all patients from baseline to the conclusion of the study was 68.5% ($p=0.011$). Six of the eight patients enrolled reported improved pain control, corresponding to decreased narcotic use during the study.

4. Abou-Assi S, Craig K, O'Keefe SJ. Hypocaloric jejunal feeding is better than total parenteral nutrition in acute pancreatitis: results of a randomized comparative study. *Am J Gastroenterol* 2002;97:2255–62.

This prospective evaluation opens the debate about whether hypocaloric jejunal feeding is superior to full calorie parenteral feeding. The study compared outcomes of patients with severe acute pancreatitis who received jejunal feedings with an elemental formula or TPN over a 12-month period. A standardized EN titration protocol that minimized the volume of nutrition patients received because of tube feeding intolerance was used. Therefore, patients in the jejunal feeding arm of the study received an average of less than 50% of goal calories and protein. This hypocaloric regimen of jejunal feedings was associated with a lesser degree of hyperglycemia, and septic complications compared to TPN. In addition, there was a shorter length of stay in patients in the jejunal feeding arm of the study. A cost-analysis identified TPN as significantly more costly per patient stay and per patient-day than EN. These data provide further evidence supporting jejunal elemental feeding in patients with severe acute pancreatitis when feasible.

5. Gupta R, Patel K, Calder PC, Yaqoob P, Primrose JN, Johnson CD. A randomized clinical trial to assess the effect of total enteral and total parenteral nutritional support on metabolic, inflammatory and oxidative markers in patients with predicted severe acute pancreatitis. *Pancreatology* 2003;3:405–13.

This prospective, randomized, nonblinded study reviewed outcomes along with oxidative markers of stress, which are thought to be the underlying pathogenic process leading to end-organ dysfunction and mortality in patients with pancreatitis. The study compared the effects of immediate jejunally administered EN with a standard polymeric formula or TPN on fatigue, oxidative stress, plasma glutamine concentrations, and endotoxemia. Participation in the EN arm of the study was associated with a shorter hospital stay, faster time to return of bowel function, and a shorter time to initiation of a full oral diet. A limitation of the study was the lack of blinding, creating the potential for bias. Despite this limitation, the study was the first to report plasma glutamine concentrations in patients with acute pancreatitis. The researchers reported insignificant changes in glutamine concentrations in both groups with no difference noted between the TPN and EN regimens. The results of this study further confirm the safety of jejunally administered EN. The benefits previously reported with elemental and semielemental formulas are now evident with standard polymeric EN as well, indicating a potential role in the setting of severe acute pancreatitis.