28 Pancreatitis

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CONTENTS

Objectives

1. Differentiate the etiology and the clinical presentation between acute and chronic pancreatitis.
2. Identify nutritional issues associated with both acute and chronic pancreatitis.
3. Determine the best route for nutrition support based on the evidence.
4. Surmount barriers to nutrition repletion in patients with pancreatitis.
5. Identify long-term nutritional issues in those with chronic pancreatitis.

Test Your Knowledge Questions

1. A consult was called on the 2nd day of hospitalization with regard to initiating nutrition support in a patient who presented with severe acute pancreatitis. The patient continued to require mechanical ventilation and a recent dynamic contrast-enhanced computed tomography (CT) scan revealed necrosis involving 30% of the pancreatic gland and a small 4-cm pseudocyst in the tail of the gland. Which of the following would you recommend?
   A. Continue nothing by mouth (NPO) status with no tube feeds, noting that the necrosis may require surgical intervention.
   B. Start the patient on parenteral nutrition (PN) because the patient is mechanically ventilated and has a pseudocyst.
   C. Place a nasojejunal tube and begin enteral tube feeds, providing no more than 10 to 20 mL/h.
   D. Place a nasojejunal tube, begin tube feeds, and advance to goal over the first 24 to 48 hours.
2. Which of the following nutrition regimens is appropriate for a patient with <2 Ranson Criteria and an APACHE II score of <9 (nonsevere), who has no pancreatic necrosis on a CT scan?
   A. Begin volume resuscitation, provide narcotic analgesia, and advance to an oral diet as soon as tolerated.
   B. Begin PN in the first 24 hours of admission because the patient has acute pain.
   C. Keep the patient NPO for at least 7 days.
   D. Use PN in the first 24 hours, then switch to an oral diet.
3. Which of the following is true?
   A. The immune response of the gut remains intact if the patient can be maintained on PN.
   B. Failure to use the gastrointestinal tract causes loss of gut integrity and exacerbates the stress response associated with pancreatitis.
   C. Loss of gut integrity may allow bacteria of gut origin to infect distant organ sites, but this is improved with bowel rest.
   D. Enteral feedings should be stopped if the ileus is noted radiographically.

Test Your Knowledge Answers

1. The correct answer is D. Complications such as pancreatic ascites, fistulas, or pseudocysts are part of the natural disease course of acute pancreatitis. Information from mostly retrospective case series indicates that the use of the enteral route is safe and allows for the resolution of these complications in most circumstances. The patient has severe pancreatitis, confirmed by 30% necrosis on a CT scan, and thus will benefit from placement on EN.
2. The correct answer is A. This patient has mild-to-moderate pancreatitis. Such patients have a mortality rate of 0% to 1.5%, a 6% rate of complications, and an 81% chance of advancing to an oral diet within 7 days. These patients may also be supported with intravenous fluid resuscitation and analgesia without added specialized nutrition support.
3. The correct answer is B. Loss of gut integrity has been demonstrated in patients hospitalized for pancreatitis who are maintained on PN and gut disuse while awaiting surgery. Over time, the villi in these patients become shortened, then lost. In contrast to pancreatitis patients kept on enteral tube feeding, pancreatitis patients placed on PN with gut disuse have been shown to have greater exposure to endotoxins and greater oxidant stress.

Background

The pancreas is a major organ involved in the digestion and absorption of food. It is a soft globular gland with no external capsule, located in the retroperitoneum between the duodenal c-loop and the hilum of the spleen. The pancreas is really two glands in one. Structurally, the endocrine portion involves the islets of Langerhans, and is responsible for producing insulin, glucagon, and somatostatin. The exocrine portion of the gland is structurally comprised of the acini and the ductal system, and is responsible for the secretion of multiple digestive enzymes including amylase, lipase, carboxypeptidase, phospholipase-α, chymotrypsin, aminopeptidase, trypsinogen, and cholesterase. The gland produces 1.0 to 2.5 L of exocrine secretions per day, which include bicarbonate, fluid volume, electrolytes, and enzymes.[1] The pancreatic exocrine secretions drain through the ductal system and join with biliary secretions in the common bile duct just prior to emptying into the duodenum through the major ampulla (ampulla of Vater). The shared tract for pancreatic and biliary secretions can be a source of pancreatitis if biliary stones or sludge occludes the common duct and prevents the drainage of pancreatic exocrine secretions. In approximately 10% of the population, the dorsal and ventral ducts do not fuse during embryonic development (pancreas divisum), and the majority of pancreatic secretions drain into the duodenum via the minor ampulla.[2] The digestive enzymes are stored in inactive precursor forms inside zymogen granules contained within the acinar cells. The activation of enzymes is prevented by protease inhibitors. The brush border enzyme enterokinase activates trypsinogen to trypsin. Once activated, trypsin is capable of activating all the other enzymes. The pancreatic exocrine secretion is influenced by a variety of stimulatory factors involving neural (vagus nerve), chemical (acid, fat, protein), mechanical (gastric distention), and hormonal agents (gastrin, secretin, vasoactive intestinal peptide, and cholecystokinin).[1] Three phases of stimulation exist. In the cephalic phase, the sight, smell, taste, and even the anticipation of food leads to the vagal stimulation of pancreatic enzyme secretion. In the gastric phase, food entering the stomach leads to the release of gastrin and the stimulation of acid output (both of which are stimulants of pancreatic secretion). Distention of the gastric wall with food leads to stimulation of the pancreas through vagal nerve input. In the intestinal phase, protein and fat entering the duodenum, along with acid, cause the release of cholecystokinin and secretin, which stimulate the release of pancreatic enzyme, fluid volume, and bicarbonate. Also in the intestinal phase, inhibitory factors are released (such as peptide YY, somatostatin, glucagon, pancreatic polypeptide, bile salts, luminal proteases, and increasing pH), all of which decrease pancreatic exocrine secretion. In the fasted state, the volume of pancreatic exocrine output is decreased, but the pancreas continues to secrete a basal flow of exocrine secretions.[1]

Acute Pancreatitis

Definition and Pathophysiology

Acute pancreatitis is an inflammatory process initiated in the pancreas with immune activation caused by active pancreatic enzymes damaging pancreatic tissue with variable involvement of other regional tissues and remote organ systems.[3-5] A poorly defined trigger event initiates the process, leading to premature activation of proteolytic digestive enzymes.[6] The initial insult results in the activation and release of trypsin into the cytoplasm of the acinar cell. This results in an amplification process, which in turn leads to a release of cytokines, inflammatory mediators, and inflammatory cell recruitment.[6] The onset of pain usually occurs 24 to 36 hours after the peak of cytokine production, with the onset of systemic manifestations and distant organ failure occurring 1 to 3 days later.[7]

Incidence

The incidence of acute pancreatitis is estimated at 40 cases per 100,000 adults in the United States, with a conservative estimate of $2.2 billion annual direct medical costs.[8] In the United States and a number of other countries, the incidence of acute pancreatitis has substantially increased in the last decade.[8-10] The increasing incidence of pancreatitis may be in part due to the increased incidence of obesity and the increased incidence of gallstone pancreatitis in older women.[9]

Etiology

Worldwide, the most common etiologies of acute pancreatitis involve alcohol (ETOH) abuse, biliary tract disease (passage of common bile duct stone), or idiopathic pancreatitis, accounting for 90% of all cases.[8-12] The distribution among these main etiologies varies with country and region, as well as the sex and age of the patients, with gallstone pancreatitis more common in women, and alcohol-related pancreatitis more common in men.[9-11] The remaining 10% of pancreatitis cases is accounted for by a variety of disorders such as pancreas divisum, trauma, hypoparathyroidism, hypercalcemia, hyperlipidemia, postendoscopic retrograde cholangiopancreatography (post-ERCP), medications, and biliary dyskinesia.[9-11] The majority of all admissions for acute pancreatitis (80% to 85%) are of mild-to-moderate severity, which is a self-limiting process with a low risk of complications (<6%) and negligible mortality. Over 80% of patients with uncomplicated, mild-to-moderate pancreatitis successfully advance to an oral diet within 1 week of hospitalization.[13-17]

Severe acute pancreatitis represents 15% to 20% of admissions, and the burden of disease in these patients is considerable.[13-17] The mean hospital length of stay is approximately 1 month, organ failure occurs in at least 16% to 33% of cases, and infection complicates the disease course in 30% to 50%. Mortality alone is 19% to 30%, but may range up to as high as 80% if organ failure or sepsis complicates the disease process.[13-17] The likelihood for advancement to an oral diet within 1 week of hospitalization for acute severe pancreatitis is close to 0%.[17] The overall disease severity is determined by the adequacy of fluid resuscitation, the presence and extent of necrosis within the gland, the presence of obesity, infection within the gland, failure of at least one organ system, and the route of nutrition support.[7,13,18,19] Pathophysiological processes outside the pancreas, primarily related to the integrity of the gastrointestinal (GI) tract, may also contribute to the level of the systemic inflammatory response syndrome (SIRS) and the rate of complications.[20-22] Severe acute pancreatitis may be identified by objective scoring systems (Acute Physiology and Chronic Health Evaluation [APACHE] II score and Ranson Criteria), and the presence of necrosis on a CT scan (Tables 28-1 to 28-3). Serum amylase or lipase greater than three times the upper limit of normal in the setting of severe abdominal pain is consistent with a diagnosis of pancreatitis. However, the severity of pancreatitis does not correlate with the degree of enzyme elevation and increased serum amylase and lipase can occur due to other intra-abdominal processes.[11,23] Additionally, the normalization (or lack of normalization) of serum amylase and lipase is not a sensitive or specific marker for the resolution of pancreatitis. A study of patients with acute pancreatitis reported that a serum lipase greater than 3 times normal the day before restarting an oral diet was significantly associated with an increased likelihood of pain relapse upon

TABLE 28-1 Differentiating Severe From Mild to Moderate Acute Pancreatitis[13,16,17]

	APACHE II ≤9 Rans Crit ≤2	APACHE II ≥10 Rans Crit ≥3
Degree of pancreatitis	Mild/moderate	Severe
CT scan	No necrosis	Necrosis
Mortality	0%	19%
PO diet in 7 days	81%	0%
Management	Supportive	EN/PN

Not exclusions: Necrosis, pseudocyst, ascites, surgery.
Exclusions: Intolerance.
CT, computed tomography; PO, by mouth; EN, enteral nutrition; PN, parenteral nutrition; Rans Crit, Ranson Criteria; APACHE, acute physiology and chronic health evaluation.

TABLE 28-2 Computed Tomography Grading System of Balthazar

Grade A	Normal-appearing pancreas
Grade B	Focal or diffuse enlargement of the pancreas
Grade C	Pancreatic gland abnormalities accompanied by mild parapancreatic inflammatory changes
Grade D	Fluid collection in a single location, usually within the anterior pararenal space
Grade E	Two or more fluid collections near the pancreas or gas either within the pancreas or within parapancreatic inflammation

Adapted with permission from Balthazar EJ, Freeny PC, van Sonneberg E. Imaging and interventions in acute pancreatitis. *Radiology*. 1994;193:297–306.

TABLE 28-3 Computed Tomography Severity Index of Balthazar and Ranson Criteria

Computed Tomography (CT) Grade	Quantity of Necrotic Pancreas
Grade A = 0	<33% necrosis = 2
Grade B = 1	
Grade C = 2	33%–50% necrosis = 4
Grade D = 3	
Grade E = 4	>50% necrosis = 6

Total Score = CT Grade (0–4) + Necrosis (0–6)
Mortality increased with score ≥7.
Reprinted by permission from Macmillan Publishers Ltd: *Am J Gastroenterol.* Banks PA. Practice guidelines in acute pancreatitis. 1997;92:377–386.

TABLE 28-4 Factors Causing Deterioration of Nutritional Status in Acute and Chronic Pancreatitis

	Acute	Chronic
Hypermetabolism	++	+
Skeletal muscle catabolism	++	+
Increased oxidative stress	++	+
Reduced oral intake	++	+
Nausea, vomiting	++	+
Errors in carbohydrate, fat metabolism	++	+
Abdominal pain	++	++
Food aversion	++	++
Protein loss (diarrhea, fistulas, inflammation)	++	++
Delayed gastric emptying	+	++
Continued ETOH abuse	+	++
Maldigestion, malabsorption	+	++
Gastric outlet obstruction	+	++

+ moderate; ++ significant; ETOH, alcohol

oral refeeding.[24] However, serum amylase and lipase after food introduction were not consistently different between the groups that tolerated oral refeeding compared to those that experienced pain. There is no data to support holding enteral feeding due to elevated serum amylase or lipase without other signs of clinical exacerbation of pancreatitis.[11,23]

The course and ultimate resolution of severe acute pancreatitis can be complicated by the effects of damage to pancreatic and surrounding tissue and the secondary response to this injury. One or more areas of the pancreatic parenchyma can become devitalized, resulting in necrotic pancreatitis. If the necrotic areas of the pancreas become infected, the risk of mortality is substantially increased, and surgical intervention is often indicated.[11] Early in the course of severe acute pancreatitis, extravasation of pancreatic fluid into the extrapancreatic space and fluid from the inflammatory and immune response to enzyme-rich pancreatic secretions can form acute peripancreatic fluid collections.[25] After several weeks, these fluid collections can be enclosed by a nonepithelialized wall of fibrinous or granulation tissue, creating a pancreatic pseudocyst.[25] Acute peripancreatic fluid collections and pseudocysts are at risk of becoming infected, and medical management frequently involves draining the fluid collections via endoscopic or percutaneous means. A circumscribed collection of obviously infected peripancreatic fluid (pus) that does not contain necrotic pancreatic tissue is termed a pancreatic abscess.[25]

Nutritional Implications of Acute Pancreatitis

Severe acute pancreatitis represents a hypermetabolic, hyperdynamic disease process very similar to sepsis (see Chapter 23).[26,27] The process generates increased oxidative stress, exaggerated catabolism, a systemic inflammatory response, and the rapid deterioration of nutritional status (Table 28-4).[3,4] Energy expenditure (see Chapter 2) may be increased by as much as 139% of that predicted by the Harris–Benedict equation.[28] More patients with acute pancreatitis are hypermetabolic than those patients with chronic pancreatitis (61% vs. 33%, respectively).[28] Sepsis complicating pancreatitis can further raise energy expenditure by a mean of 15%.[28] The catabolic stress state generates increased muscle catabolism and proteolysis, causing the loss of lean muscle mass. Accelerated ureagenesis occurs, and glutamine levels are decreased both in muscle and in serum.[29] A number of consequences in addition to exaggerated catabolism promote the deterioration of nutritional status. Reduced oral intake can occur from abdominal pain, food aversion, nausea, vomiting, gastric atony with paralytic ileus, continued ethanol abuse, or partial obstruction of the duodenum from enlargement of the pancreatic gland. Nutrient losses may be increased because of maldigestion from reduced enzyme output, malabsorption of luminal nutrients, or excessive protein loss caused by diarrhea, pancreatic fistulas, or inflammation of peritoneal and retroperitoneal surfaces. No studies have compared the effect of different calorie or protein provisions on patient outcomes in acute pancreatitis. Nutrition goals in the early stage of severe pancreatitis are to avoid overfeeding and provide adequate protein to support acute-phase protein synthesis (Table 28-6). Calorie provision may need to be increased if recurrent infections maintain elevated energy expenditure, or to support increased physical activity and positive nitrogen balance when the acute phase of illness has passed.

Stress hyperglycemia and insulin resistance occur in 40% to 90% of patients with severe acute pancreatitis.[30,31] Insulin resistance and persistent gluconeogenesis are a result of critical illness (see Chapter 23) and can be compounded in pancreatitis when there is sufficient necrosis of parenchymal tissue with decreased insulin production.[31] Errors in fat metabolism (see Chapter 4) with hypertriglyceridemia occur in 12% to 15% of cases.[29,31,32] Hypertriglyceridemia is frequently seen in association with inadequate glucose control due to the downregulation of lipoprotein lipase in hyperglycemia.[33] Achieving adequate glucose control is essential to decrease serum triglyceride levels when hypertriglyceridemia is secondary to poor glucose control.[33,34] Electrolyte and micronutrient alterations (see Chapters 7 and 8) are common, especially hypocalcemia, which can occur in up to 25% of cases.[32] A reduction in calcium levels are related to decreased parathyroid hormone release, increased calcitonin, decreased magnesium levels, hypoalbuminemia, and saponification of

calcium with unabsorbed free fatty acids. Long-term ethanol abuse can lead to decreases in zinc, magnesium, thiamin, and folate levels.[29,31,32]

Role of the Gut in Systemic Inflammatory Response Syndrome and Benefits of Enteral Nutrition

The provision of enteral nutrition (EN) to patients with severe acute pancreatitis helps maintain gut integrity by preventing increases in permeability and keeping the functional tight junctions between the intestinal epithelial cells closed (Table 28-5).[35-37] EN stimulates blood flow to the gut, which prevents ischemia/reperfusion injury. EN stimulates the release of secretory immunoglobulin A (IgA) and bile salts, which coat bacteria and prevent their adherence to the intestinal epithelium.[35-37] EN maintains the mass of gut-associated lymphoid tissue (GALT), which in turn supports the mass of mucosal-associated lymphoid tissue (MALT) at distant organ sites.[35-39] EN supports the role of commensal bacteria, which prevent colonization of the gut by pathogenic organisms.[35,40] Colonization of the gut with commensal organisms may reduce the likelihood for contact-dependent activation of intestinal epithelial cells by pathogenic organisms. Such a process can lead to increases in gut permeability from cell apoptosis and opening of the tight junctions, activation of neutrophils, and the release of inflammatory cytokines.[35,40] A small scale study suggested that a probiotic preparation may potentiate the action of commensal bacteria.[41] However, a large multicenter randomized study demonstrated no decrease in infectious complications and significantly increased mortality from ischemic bowel from a high-dose multispecies probiotic preparation in severe pancreatitis.[42]

A provision of EN attenuates the stress response compared to patients who receive parenteral nutrition (PN).[20] Patients placed on EN with severe acute pancreatitis demonstrate increases in antioxidant capacity, faster decreases in C-reactive protein levels, and faster resolution of SIRS compared to patients who are placed on PN.[20] Time to resolution of the disease process, as evidenced by the resolution of abdominal pain, the near normalization of amylase, and the successful advancement to a clear liquid diet is reduced by half with the use of EN compared to PN.[43] As a result of the differential effect of the gut in response to starvation versus feeding, it should not be surprising that the provision of EN has a dramatic impact on patient outcome compared to a provision of PN.[22,44] Two meta-analyses, involving seven prospective randomized trials in patients admitted for acute pancreatitis, showed that the use of EN reduces infection by as much as 52% ($p<.05$), hospital length of stay by as much as 4 days ($p<.05$), the need for surgical intervention by as much as 52% ($p<.05$), and a trend toward reduced organ failure by as much as 41% ($p=.06$), when compared to the use of PN.[22,44] No difference in mortality was seen between the two routes of nutrition support.[22,44]

TABLE 28-5 Benefits of Early Enteral Feeding in Acute Severe Pancreatitis

Maintains gut integrity (reduce bacterial challenge)
Sets the tone for systemic immunity (downregulate immune response)
Attenuates oxidative stress
Lessens disease severity
Promotes a faster resolution of the disease process
Reduces complications (less infections and need for surgical interventions, shorter hospital length of stays, and possibly less multiple organ failures)

The Importance of Pancreatic Rest

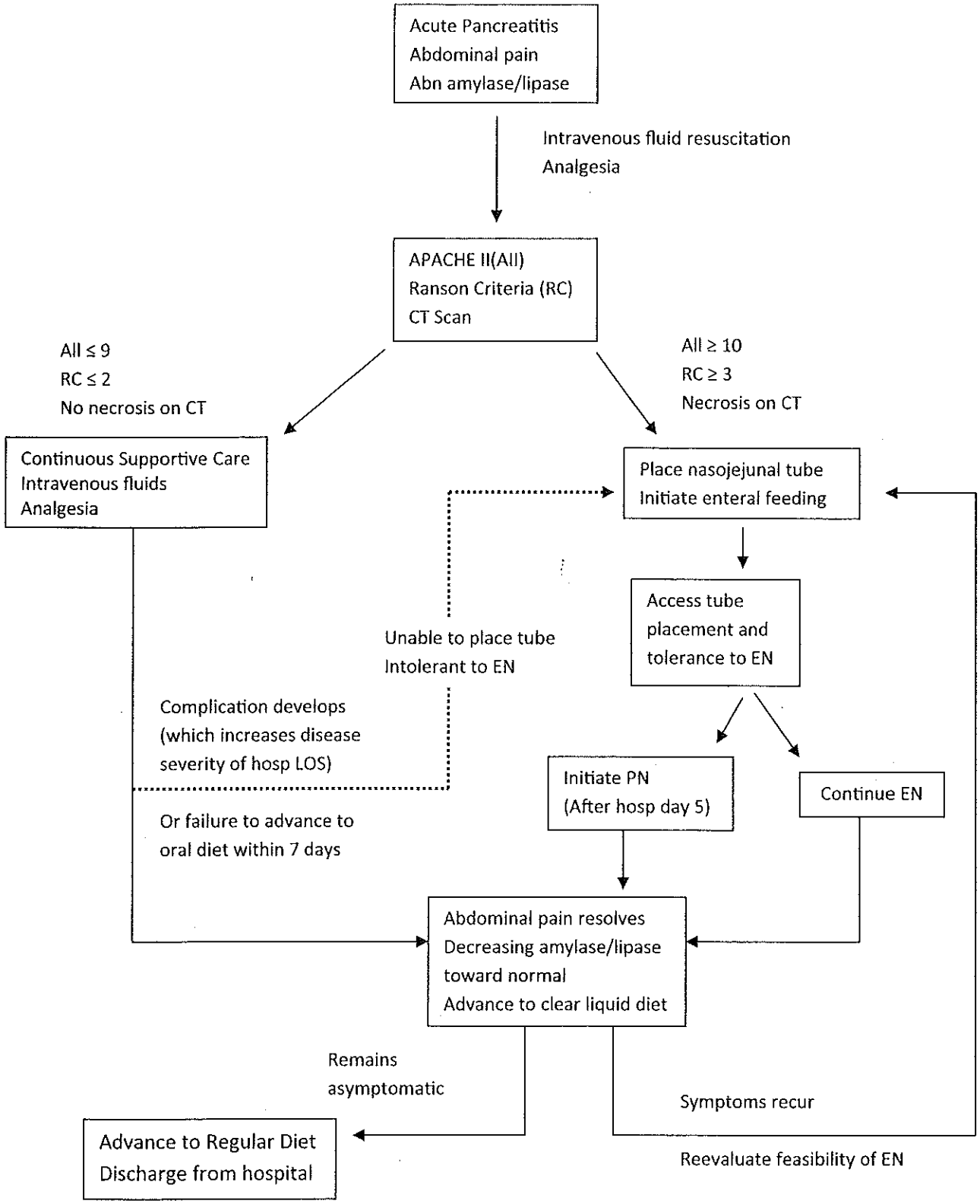
The clinician's perspective on the need for pancreatic rest and its overall clinical significance has changed dramatically over the last 15 years. In the past, early use of the gut and the advancement to an oral diet was thought to increase the risk for late complications, primarily pancreatic abscess. Prospective randomized trials have failed to confirm this fear.[22,44] Instead, the clinical consequences of early use of the enteral route seem to involve one of three possible scenarios: a clinically silent increase in pancreatic enzyme output,[45] an uncomplicated exacerbation of symptoms (which occurs in approximately 21% of patients),[45,46] or an exacerbation of the disease process itself with an increase in SIRS (in 4% of cases).[45,46] Usually subtle changes in the manner by which EN is provided are sufficient to reduce the exacerbation, promote tolerance, and continue feeding without an overall deleterious impact on the patient. Experience from the literature suggests that efforts to promote pancreatic rest as the sole management strategy to treat pancreatitis (through the use of nasogastric suction, somastatin, acid-reducing agents, etc.) is ineffective and does not have an impact on patient outcomes.[29] It seems now that reducing pancreatic enzyme output to basal unstimulated levels is not required to allow for the resolution of inflammation within the gland, but that reducing output to subclinical levels may be sufficient. The concept of putting the pancreas to rest and using the gut are not incompatible; both may be accomplished simultaneously in the same patient.

Providing Nutritional Support

The options for nutritional support in patients with acute pancreatitis are threefold: the provision of EN, the placement on PN, or the use of standard therapy (STD) in which no specialized nutritional support is provided (and patients are on their own to advance to an oral diet with the delivery of food on a tray). The choice among these options is determined by disease severity, timing, and tolerance (Figure 28-1 and Tables 28-6 and 28-7).

The patients with the greatest need for specialized nutritional support, who are most likely to experience a benefit in a clinical outcome from the provision of EN, are those patients with greater severity of pancreatitis. Intestinal permeability is increased in patients with severe pancreatitis, compared to those patients with mild pancreatitis (and controls with no pancreatic disease).[47] Patients with severe pancreatitis complicated by organ failure have greater increases in permeability above that seen in patients with severe but uncomplicated

FIGURE 28-1 Algorithm for the Nutritional Management of Acute Pancreatitis



APACHE, acute physiology and chronic health evaluation; CT, computerized tomography; EN, enteral nutrition; PN, parenteral nutrition; hosp, hospital; LOS, length of stay;

TABLE 28-6 The Initiation of Enteral Nutrition in Severe Acute Pancreatitis

Initiate nutrition support by continuous infusion over 24 h/d to meet energy and protein requirements
Estimated energy requirements 25 kcal/kg/d
Estimated protein requirements 1.5 g/kg/d
Measure energy requirements with indirect calorimetry when possible
Provide mixed fuel regimen (protein, fat, and carbohydrate)
Monitor tolerance closely

TABLE 28-7 The Selection of Enteral Formula in Severe Acute Pancreatitis

- Standard polymeric formula: May be used if tip of feeding tube is low enough (below ligament of Treitz) in the GI tract.
- Evidence of intolerance (increase in pain, fever, or white blood cell [WBC] count in association with increases in serum amylase, lipase): Switch to elemental very low fat formula or switch to a semielemental formula with small peptides and medium-chain triglycerides.
- Evidence of malassimilation (diarrhea and/or steatorrhea): Switch to semielemental formula with small peptides and medium-chain triglycerides.

pancreatitis.[48] Out of the first four prospective trials of EN versus PN in acute pancreatitis, the greater the percentage of patients with severe pancreatitis, the more likely the route of feeding had an impact on outcome.[20,43,46,49] In the McClave study,[46] where 19% of patients had severe pancreatitis, there was no difference in any outcome parameters between the two groups. In the Windsor[20] and the Abou-Assi studies,[43] where 35% to 38% of patients had severe pancreatitis, there was faster resolution of SIRS and a shorter duration of time to the resolution of the disease process in patients receiving EN compared to those on PN. Only in a fourth study by Kalfarentzos et al.,[48] in which 100% of patients had severe pancreatitis, were traditional outcome parameters such as overall complications and septic morbidity reduced significantly with use of EN compared to PN. These studies indicate that EN is clearly the first choice over PN in patients with severe acute pancreatitis. Unfortunately, little data exist specifically in the population of patients with acute pancreatitis that show EN has a favorable impact on outcome compared to STD (no specialized nutritional support). In one small study in patients admitted with acute pancreatitis, Powell et al.[49] randomized patients to EN versus STD. A reduction in the overall stress response in those patients receiving EN was suggested by decreases in tumor necrosis factor (TNF), interleukin-6 (IL-6), and C-reactive protein levels as compared to those patients randomized to STD, but the duration of therapy was only 4 days, and the differences did not reach statistical significance.[49] In a meta-analyses of two studies by Pupelis et al.,[22,50,51] patients requiring surgery for complications of acute pancreatitis were randomized to EN versus STD postoperatively. Aggregating from these two studies involving a total of 71 patients, a trend toward reduced mortality (by as much as 74%) was seen in those patients receiving enteral nutrition (EN) compared to those randomized to STD (RR = 0.26; 95% CI 0.06; 1.09; $p - .06$).[22]

An objective scoring system may be used to identify patients with more severe pancreatitis, who are therefore candidates for specialized nutritional support (Figure 28-1). An APACHE II score of ≥10 and the presence of ≥3 Ranson Criteria identify those patients with severe necrotizing pancreatitis.[14–16] These are the patients in whom the provision of EN is most likely to have an impact on outcome. These patients should undergo placement of enteral access and have EN initiated within 48 hours of admission. Patients with mild-to-moderate pancreatitis may be identified by APACHE II scores of ≤9 and the presence of ≤2 Ranson Criteria.[13–16] These patients would not be expected to have outcomes affected by the provision of EN, and may be supported alone with STD, intravenous fluid resuscitation, and the provision of narcotic analgesia. Not all patients tolerate EN. Although variable from one institution to the next, a certain percentage of patients may still require the provision of PN. Placement on PN should be reserved for those patients with severe disease in whom the provision of EN is poorly tolerated or not feasible (see Chapter 14). The timing of specialized nutrition support is critical for both EN (which should be provided within the first 48 to 72 hours of admission), and PN (where initiation of therapy may need to be delayed until after the 5th day of hospitalization). In an early prospective randomized trial, the provision of PN within the first 24 hours of admission caused net harm compared to placement on STD.[17] The provision of PN in patients with mild pancreatitis resulted in a hospital length of stay that was 1 week longer and a rate of central line catheter infection that was tenfold greater than for those patients receiving intravenous fluid volume support without specialized nutrition therapy.[17] In a later study in China, patients were not randomized to PN or STD until after a complete fluid resuscitation.[52] Patients were then randomized, and nutrition was started within 48 hours of completion of that resuscitative process. The provision of PN at this point (presumably several days later, past the peak of inflammation) had a favorable impact on outcome by reducing mortality, overall complications, pancreatic infection, and hospital length of stay, compared to a group receiving STD (outcome was even better for a third group of patients in the study who were randomized to receive PN supplemented with parenteral glutamine).[52]

Provision of Enteral Nutrition Support

The safety of jejunal EN is now well documented in 10 prospective randomized trials.[20,43,46,48,53–58] Every study end point related to the clinical outcome (days to normalization of amylase, days to oral diet, length of hospitalization, length of stay in the ICU, percent of nosocomial infection, and mortality) is equal to or better in the group receiving EN compared to those randomized to PN.[22] Complications of pancreatitis (such as the presence of a pseudocyst, abscess, or ascites) are not a contraindication to EN. EN may continue to be provided as long as tolerance is demonstrated.

Nasogastric Versus Nasojejunal

Several studies have suggested that nasogastric feeding may be an effective means to provide nutrition support to patients with severe acute pancreatitis.[59,60] However, there continues to be some controversy about the appropriateness of gastric enteral feeding for severe pancreatitis. There is concern that several studies compared gastric feeding with distal duodenal, not jejunal feeding.[61] Duodenal feeding may actually result in greater pancreatic stimulation than gastric feeding.[62,63] Additionally, in one study,[59] the median pain score and use of narcotic pain medications was near zero by the 3rd day of feeding (study day 5) in both groups, which appears inconsistent with severe pancreatitis and the relatively high mortality rate in the study. In the sole study that has randomized patients to receive either gastric EN or PN, there were significantly more complications in the EN group, despite the greater incidence of hyperglycemia in the PN group.[64] Despite the ongoing questions, there does appear to be a number of patients that apparently tolerated early semielemental gastric EN. Gastric feeding access is easier to achieve than jejunal placed tubes and has the potential advantage of allowing earlier EN in severe pancreatitis. Currently, the preponderance of data supporting EN over PN in severe pancreatitis have provided EN beyond the ligament of Treitz (LOT), but there is a clear need for additional studies of gastric EN.

Fluoroscopy and endoscopy are frequently used to assist and ensure the placement of feeding tubes due to the difficulty in achieving blind placement of tubes beyond the LOT. Magnetic guidance, the use of modified feeding tubes that generate an electromagnetic signal recognized by an external receiver, and self-advancing feeding tubes have all been reported to assist with small bowel feeding tube placement.[65-67] However, there is limited data about their effectiveness for placement of feeding tubes beyond the LOT, especially in patients prone to duodenal compression from an inflamed pancreas. It is advisable for clinicians to recognize the location of feeding ports in relation to the tip of the feeding tube used at their facility. Feeding tubes that have feeding ports proximal to the tip (frequently seen with weighted tubes) may appear to be positioned beyond the LOT, whereas in reality, the feeding ports remain in the duodenum.

Formula Choices for Enteral Nutrition

Standard polymeric enteral feeding formulas may be used when feeding distal to the LOT. Several of the studies that have demonstrated the superiority of jejunal EN over PN used polymeric formulas,[20,51,68] and when polymeric formulas were infused 40 to 60 cm distal to LOT there was actually an inhibition of pancreatic secretions compared to PN.[63] However, patients with extensive pancreatic necrosis or those demonstrating signs of maldigestion/malabsorption may benefit from a semielemental or elemental feeding after the most common causes of diarrhea (sorbitol-containing medications and *Clostridium difficile*) are excluded. A review of 127 patients with complicated pancreatitis receiving jejunal feeding documented that 30% of the patients tested had a positive fecal fat result indicating steatorrhea.[69]

Troubleshooting Enteral Nutrition

Patients that experience intolerance to EN infusion (increased abdominal pain, exacerbation of SIRS) should have the position of the feeding tube rechecked or advanced further beyond the LOT. In the study by McClave,[46] a patient tolerant of a jejunal infusion of formula flared with an exacerbation of SIRS when the same formula was infused into the stomach (after the tip of the tube was displaced proximally in the GI tract). Patients with severe pancreatitis frequently experience abdominal pain, and it is important to distinguish persistent pain from pancreatitis from acute increase in pain associated with starting EN initiation when evaluating tolerance.

However, increased nausea due to pain medications, functional gastric outlet obstructions, or an ileal brake from jejunal feeding should not be a contraindication to continued jejunal EN.[72] Double lumen tubes, which allow feeding through a distal opening and simultaneous gastric decompression through the proximal opening, may be useful to decrease nausea without the need for a second nasal tube for nasogastric decompression. One potential disadvantage of double lumen tubes is that in order to maintain an external diameter that is relatively comfortable for the patient (14 to 16 Fr), the jejunal portion of the tube is usually 6 to 9 Fr and may be prone to frequent clogging.

The institutional variation in the tolerance of EN in pancreatitis may be related to local expertise in achieving enteral access, the existence of a multidisciplinary nutrition support team, and the aggressiveness with which the institution initiates EN. At one institution, only 5 patients out of 16 randomized to EN demonstrated problems with ileus (requiring decreases in the rate of infusion but not of the cessation of feeding).[20] In a separate institution in the same city, attempts to initiate EN were successful in only 53% of patients admitted for pancreatitis; 47% were unsuccessful and had to be placed on PN or STD.[72] The duration of ileus before the initiation of EN may be a factor in tolerance. In a study from Portugal, patients in whom the duration of ileus was $\geq$6 days did not tolerate EN and had to be placed on PN.[48] If the duration of ileus was limited to $\leq$5 days, 50% of patients tolerated EN, whereas ileus limited to $\leq$2 days resulted in a 92% tolerance of EN.[72,73]

Parenteral Nutrition

Although the majority of patients appear to tolerate EN in severe acute pancreatitis, there are patients in whom EN is not feasible and PN is required to prevent severe malnutrition. Persistent ileus or small bowel obstruction, especially in patients admitted with compromised nutrition status, are indications for PN. Additionally, there are occasional patients that experience exacerbations of pancreatitis symptoms even with a proper jejunal placement of feeding tubes and elemental EN infusion. In two different studies, some patients failed to tolerate EN in a situation where the tube was placed well below the LOT.[43,46] The physiologic reasons why some individual patients are unable to tolerate EN in pancreatitis remains unclear, but EN is considered contraindicated if it is clearly exacerbating disease morbidity.

Intravenous Lipid Emulsions

Intravenous lipid emulsions do not exacerbate the symptoms of pancreatitis that has not been caused by hypertriglyceridemia, and a mixed fuel source (carbohydrate CHO, protein, lipid) PN is recommended.[74,75] Hypertriglyceride-induced pancreatitis generally occurs only in susceptible individuals with triglyceride >1000 mg/dL, and a lipid emulsion can be safely restarted when triglycerides decrease below 400 mg/dL. When the quantity of lipids in PN is limited to less than 1 g of fat per kilogram, and glucose control is maintained, the occurrence of hypertriglyceridemia during PN is limited.[76] When hypertriglyceridemia occurs in the setting of pancreatitis, it is frequently related to familial dyslipidemia and/or hyperglycemia.[77]

The Resumption of Oral Intake

There is limited data to guide the resumption of oral intake following an episode of acute pancreatitis. Most clinicians take into consideration the presence or absence of pain, the severity of pancreatitis, biochemical markers, and radiologic improvement based on a CT scan. Pancreatitis that has been complicated by a pseudocyst or sterile necrosis is increasingly managed with conservative therapy. It is unclear if extending the period of nil per oris (nothing by mouth) with longer term jejunal feeding offers benefits over standard care in the conservative management of complicated pancreatitis. Some facilities have reported favorable outcomes in retrospective reviews with long-term access for jejunal feeding in patients with more chronic or complicated pancreatitis.[69,78]

In mild acute pancreatitis, there does not appear to be any advantage to starting diets with liquids or a low-fat oral intake.[79–81] In fact, it appears that allowing patients free-choice regarding when to begin oral intake and the self-selection of foods may offer the advantage of decreasing the length of hospitalization without increasing the rate of relapse or abdominal pain.[79–81] (Practice Scenario 28-1)

Practice Scenario 28-1

Question: How should the patient with severe acute pancreatitis receive nutrition support?

Scenario: A 57-year-old female is admitted with a sudden acute onset of bilateral upper quadrant abdominal pain, nausea, and vomiting accompanied by fever. Initial laboratory results reveal an elevated amylase and lipase, suggesting acute pancreatitis. Over the first 12 hours of hospitalization, the patient developed respiratory distress and hypoxemia, requiring placement on mechanical ventilation. Height, 5'2"; weight, 165 lb (calculated body mass index [BMI], 30.2). Temperature was elevated at 103°F, with a blood pressure of 180/70 mm Hg, and a heart rate of 135. The patient's abdomen is obese, distended, and bowel sounds are hypoactive. She has voluntary guarding. Examination of her extremities reveal mild edema. Current medications include acetaminophen, a proton pump inhibitor, meperidine, and promethazine hydrochloride. Initial laboratories reveal an elevated WBC of 21,000, hemoglobin of 10.5, hematocrit of 32.8, blood urea nitrogen (BUN) of 55 mg/dl, creatinine of 2.5 mg/dL, serum potassium of 3.4 mmol/L, and sodium of 155 mmol/L. Her glucose is 186 mg/dL, albumin is 3.0 g/dL, and calcium is 7.8 mg/dL. The patient's serum lactate dehydrogenase was elevated at 400 IU/L. The patient underwent a CT scan, which revealed an enlarged edematous pancreas, necrosis involving 35% of the gland, surrounding inflammatory changes, and free fluid in the lesser sac. An abdominal ultrasound revealed a prominent common bile duct with possible choledocholithiasis. The patient's urinalysis was remarkable for increased specific gravity, but no evidence of infection. Blood cultures and urine cultures were obtained and were negative. The patient was admitted to the intensive care unit (ICU), and a central line was placed and started on intravenous volume resuscitation with normal saline.

Intervention: On day 2 of admission, the patient had a small bore orojejunal tube placed via fluoroscopy with the feeding ports distal to the LOT.

Answer: With a feeding tube placed well below the LOT, a standard polymeric feeding formula may be initiated. Hypocaloric protein-sparing feedings would be appropriate in a patient with a BMI of 30, and the use of a high-nitrogen 1 calorie per milligram formula would help to meet calorie-protein goals without excessive protein supplement administration. A reduced-electrolyte "renal" formulation should not be necessary unless clinically relevant hyperkalemia occurs on a standard formula due to the patient's renal compromise; protein should not be restricted. Considering the severity of the pancreatitis and extensive pancreatic necrosis, it is possible that the patient may require a semielemental or very low fat elemental formula to prevent steatorrhea. If the patient experiences distention or nausea, the decompression of endogenous gastric and/or biliary secretions with a nasogastric or orogastric tube may be necessary.

Rationale: This patient presents with classic, acute pancreatitis as evidenced by abdominal pain, elevated amylase and lipase, and an early SIRS response. The patient had three Ranson Criteria (WBC >16,000, lactate dehydrogenase >350, and serum calcium level <8.0 mg/dL) and the admission APACHE II score was 16, indicating severe pancreatitis. There was also >30% necrosis of the gland per the CT scan and evidence of multiple organ failure. The severe and complicated pancreatitis indicates that the patient has a 40% chance of having a complication, a 6% chance of mortality, and her chance of advancing successfully to an oral diet within 7 days was close to zero. This patient's clinical outcome could have a favorable impact by the placement of a jejunal tube and the initiation of EN. If endoscopic intervention is delayed due to critical illness, then the fluoroscopic placement of a feeding tube would be appropriate to initiate timely enteral nutrition.

Chronic Pancreatitis

Introduction

Chronic pancreatitis (CP) is an insidious and very debilitating disorder that comes at a very high cost—socially, financially,

and to the individual experiencing it. The healthcare cost is difficult to quantify given the myriad of comorbidities (diabetes, alcoholic liver disease, smoking related diseases, etc.) associated with CP. The total estimated cost for all pancreatitis for nonfederal institutions and physicians was reported as $3.7 billion in 2004. The number of hospital admissions and ambulatory visits where pancreatitis was listed as the first diagnosis were 277,000 and 475,000, respectively. Pancreatitis ranked eighth in overall healthcare costs to society and seventh in hospital admissions and charges among all digestive disorders.[82] CP has a high mortality rate of approximately 50% within 20 to 25 years of onset[83]; pancreatic cancer looms at 3 to 5 times the expected incidence.[84] There is no consensus on the best treatment for CP; therefore, primary treatment is aimed at symptom control. Abdominal pain is one of the outstanding features of CP; hence, analgesia is frontline treatment. Pain management and problems arising from use of pain medications are often a component of the care of patients with CP. Newer therapies, however, such as the use of micronutrients and antioxidants, are emerging.[85]

Epidemiology

The reported yearly incidence of CP varies considerably and ranges from 3 to 8 new cases per 100,000. [85] There is a significant gender difference in those with CP, which is by far predominated by men and reported to be between 73% to 91%.[83] This is no surprise given the high proportion of men with alcoholism. In fact, 90% to 95% of alcohol-induced CP may be male, presenting in the 4th or 5th decade of life. The only country where this sex difference does not hold true is in the United States, where there is almost an even split between the sexes in hospital admissions for CP.[83] Overall, the data suggest that the incidence of CP is rising worldwide; it is surmised that rising alcohol use in addition to an improvement in diagnostic techniques are responsible. Smoking is associated with a fourfold increase in the risk of acute pancreatitis progressing to CP.[86]

Etiology

Although CP has many origins (Table 28-8), the clinical presentation of CP reveals a geographical variation, with alcohol being the most common etiology in the industrialized world, and tropical or idiopathic forms dominating the developing world. Although alcohol has long been touted as the leading cause of CP worldwide, less than 10% of those who drink in excess develop the disease process.[83] In the United States, chronic alcohol consumption was thought to be the leading cause of CP; however, a new hypothesis is emerging, the sentinel acute pancreatitis event (SAPE) hypothesis, which suggests acute pancreatitis, and especially recurrent bouts, are prerequisites for developing CP—an "end-stage" if you will, of recurrent AP.[87] A large, multicenter questionnaire was completed by physicians and patients to evaluate the combinations of risk factors, which together, defined an immune-medicated pathologic process or pathway.[87] Those who present with CP, presumably as a result of alcohol consumption, report an intake of ≥50 to 150 g/day over 6 to 12 years.[83,88] See Table 28-9 for grams of alcohol in commonly consumed libations.

TABLE 28-8 Causative Factors[88]

Toxic Xenobiotics
- Alcohol
- Cigarette smoke
- Occupational volatile hydrocarbons
- Drugs: valproate, phenacetin, thiazide, estrogen, azathioprine

Endogenous
- Hypercalcemia, hyperparathyroidism
- Hyperlipidemia, lipoprotein lipase deficiency
- Chronic renal failure

Infection or Infestation
- HIV, mumps virus, Coxsackie virus
- *Echinococcus, Cryptosporidium*

Genetic[a]
- *CFTR* mutation
- *PRSS1* mutation
- *SPINK1* mutation

Obstruction of Main Pancreatic Duct
- Cancer
- Posttraumatic scarring
- Postduct destruction in a severe attack
- Pancreatic divisum

Recurrent Acute Pancreatitis
- Postnecrotic
- Vascular diseases/ischemic
- Postirradiation

Autoimmune
- Isolated autoimmune chronic pancreatitis
- Syndromic autoimmune chronic pancreatitis (Sjögren syndrome, inflammatory bowel disease, and primary biliary cirrhosis-associated chronic pancreatitis)

Miscellaneous
- Gallstones
- Posttransplant
- Postirradiation
- Vascular disease
- ERCP-induced

Idiopathic
- Early or late onset
- Tropical

CFTR, cystic fibrosis transmembrane conductance regulator; PRSS1, protease serine cationic trypsinogen; SPINK1, serine protease inhibitor Kazal-type 1; ERCP, endoscopic retrograde cholangiopancreatography.
[a]Other, less common mutations have been described.
Adapted from *The Lancet*, 377, Braganza JM, Lee SH, McCloy RF, McMahon MJ, Chronic Pancreatitis, 1184–1197. Copyright 2011, with permission from Elsevier.

TABLE 28-9 Alcohol Content of Common Libations

Beverage	Alcohol (%)	g/100 mL (3.3 oz)
Beers (lager)	3.2–4	3.2–4
Ales	4.5	4.5
Porter	6	6
Stout	6–8	6–8
Malt Liquor	3.2–7	3.2–7
Sake	14–16	14–16
Table wines	7.1–14	7.1–14
Sparkling wines	8–14	8–14
Brandies	40–43	40–43
Whiskies	40–75	40–75
Vodkas	40–50	40–50
Gin	40–48.5	40–48.5
Rum	40–95	40–95
Tequila	45–50.5	–50.5

Hypertriglyceridemia

Hypertriglyceridemia, specifically a triglyceride (TG) level >1000 mg/dL, is associated with pancreatitis; recurrent bouts are reported if TG are not adequately controlled.[89,90] Patients at particular risk for hypertriglyceride-induced pancreatitis include those with type I, IV, or V hyperlipoproteinemia, diabetes mellitus (DM), ETOH abuse, obesity, and pregnancy. The age of onset also provides clues as to the etiology of CP. The median age of onset for alcoholic, idiopathic, familial, and tropical CP is reported as 40.8, 27.0, 18.8, and 9.8 years, respectively.[83]

Pathophysiology and Clinical Presentation

CP is a progressive, inflammatory process in which pancreatic tissue is slowly destroyed and replaced by fibrotic, calcified tissue. Traditionally, CP was considered distinctly different from acute pancreatitis, an event after which the pancreas fully recovers. CP, however, was thought to be a condition characterized by permanent and irreversible damage. Now it is thought that CP may be on a continuum where recurrent acute pancreatic injury is occurring (either overtly or subclinically), but may be subclinical with genetics and the environment playing a significant role.[87] As structural changes occur over time, functional alterations follow, primarily endocrine and exocrine.

The hallmark features of CP include abdominal pain (85% to 90% of cases); in some, episodes of acute pain and inflammation occur in a previously injured pancreas ("acute on chronic"). Pain can be intermittent, constant, or superimposed with acute flares. Some will have weight loss from an inability to eat, malabsorption, and poorly controlled diabetes, if present, and there are some who may be asymptomatic for years. Diagnosis relies on symptoms, radiographic evidence, CT scans, and elevated amylase and lipase (in those who have enough functioning pancreatic tissue left to synthesize and secrete it).[88] Complications of CP include bile duct stricture, duodenal stricture, portal hypertension, pseudocysts, pancreatic fistulas and ascites; mortality is nearly 50% within 20 to 25 years of the disease onset.[91]

Factors Promoting Protein/Calorie Malnutrition

Recurrent flares of CP invoke similar mechanisms for promoting the deterioration of nutritional status as seen in acute pancreatitis, with increased caloric and protein requirements, decreased oral intake, and greater nutrient losses.[92] However, multiple problems develop, specifically as a complication of CP and set the stage for progressive malnutrition (Table 28-10). Between bouts or flares of CP, persistent abdominal pain may generate anorexia, decreased intake due to fear of exacerbating symptoms, fat-restricted diets (either self-imposed or by healthcare professionals),[93,94] and weight loss.[95] Continued alcohol consumption is an independent risk factor itself in promoting malnutrition. Gastric dysmotility is common with up to 44% of patients having gastroparesis.[96] A large pseudocyst, diffuse inflammation, or scarring in the head of the gland can contribute to gastric outlet obstruction. Exocrine insufficiency occurs in about 50% of patients, developing 10 to 12 years after the onset of CP, and 90% or more of the exocrine pancreatic tissue is destroyed. It manifests clinically as diarrhea, steatorrhea, and malassimilation.[97] Steatorrhea is defined as the quantitative appearance of >7 g of fat per day after consuming or having infused 100 g of fat. Patients need to consume enough dietary fat before and during a fecal fat test to avoid false negative results (one must receive enteral fat in order to malabsorb it). It is important to note, however, that these patients may be on enough narcotic analgesia to prevent diarrhea,

TABLE 28-10 Factors Promoting Protein/Calorie Malnutrition in Patients with Chronic Pancreatitis[110]

- Recurrent flares/hospital admissions and NPO status
- Abdominal pain
- Increased caloric requirements, especially in those with low BMI, have higher lean body mass/fat ratio
- Anorexia
- Pancreatic insufficiency
- Alterations in bile salt efficacy due to decreased bicarbonate secretion in those not acid suppressed
- Motility changes from inflammation, duodenal compression, scarring
- Gastroparesis from hyperglycemia
- Continued alcohol misuse
- Small bowel bacterial overgrowth
- Self-imposed dietary restrictions caused by the fear of inducing pain
- Fat restricted diets

NPO, nothing by mouth; BMI, body mass index. Used with permission from the University of Virginia Health System Nutrition Support Traineeship Manual, July 2010.

and constipation may occur. Carbohydrate absorption is usually fairly well preserved. Due to decreased bicarbonate output from the pancreas with a resultant loss of gastric acid neutralization, the bile salts and what few pancreatic enzymes that are secreted become inactivated by gastric acid, which serves to worsen the maldigestion.[98] Small bowel bacterial overgrowth has been reported in 34% to 40% of patients with chronic pancreatitis.[99,100,101]

Maldigestion in itself increases the risk for vitamin and trace element deficiencies. Vitamin B12 deficiency is fairly common, because of the lack of production of the proteolytic enzyme secreted from the pancreas that is required to cleave the R-protein from intrinsic factor.[102] Patients with CP are at risk for the malabsorption of fat-soluble vitamins (A, D, E, and K), but isolated deficiencies are somewhat rare. The bone mineral density of patients with CP has been shown to be markedly decreased compared to controls.[103,104] In another study, low trauma fracture was found to be comparable with high-risk GI disease states that have osteoporosis screening guidelines in place.[105] Consider a dual-emission X-ray absorptiometry (DXA, previously DEXA) at the diagnosis of CP to identify those who might require more aggressive intervention to maximize bone health.

Persistent or intermittent hypermetabolism occurs in one-third of patients and may be a factor in continued weight loss. In one study, 65% of patients with CP who had weight loss showed an energy expenditure >110% of what was predicted by the Harris–Benedict equation, whereas only 20% of the CP patients with normal weight demonstrated such findings.[106] The increased energy expenditure may be related to continued ethanol ingestion or the persistent secretion of cytokines and catabolic hormones.

Diabetes mellitus is the major late sequelae of CP and is an independent risk factor for mortality in patients with CP. In a prospective study of 500 patients with CP, the cumulative rates of the appearance of diabetes mellitus since the onset of CP were 50% and 83% at 10 and 25 years, respectively; insulin requirement was 26% and 53% at 10 and 25 years, respectively.[107] These patients with CP behave as if they have "brittle" diabetes, with wildly fluctuating glucose levels and a propensity for hypoglycemia.[97,108] Diabetes alone may contribute further to underlying gastroparesis.

Several mechanisms may be involved in the persistent pain experienced by patients with CP.[109] Because of distorted ductal anatomy resulting from scar tissue, pancreatic stimulation may lead to elevated pancreatic ductal pressure. Increases in ductal pressure may, in turn, compromise blood flow to pancreatic parenchyma, producing ischemia and worsening abdominal pain. The obstruction of normal flow through the pancreatic duct may force enzymes into the parenchyma, resulting in autodigestion of the pancreatic tissue.[109]

Treatment

The causes of CP are diverse (Table 28-8), and as such, it is important that the underlying cause be identified to target interventions accordingly in an effort to reduce recurrent injury and delay or to stop further damage to the pancreas from occurring. In order to successfully maintain or replete the patient with CP, absolute abstinence from alcohol in those misusers, and sufficient pain control is necessary. In patients who are able to abstain from alcohol, symptoms tend to progress less rapidly, 75% of whom may expect to achieve symptomatic relief with the cessation of alcohol.[111] Pancreatic enzyme supplementation in high doses has been evaluated in an effort to provide pain relief in patients with CP. However, evidence to date has failed to show consistent benefit.[112]

Oxidative stress has been implicated in the pathophysiology of CP and is theorized to initiate cell damage in the following manner: either directly by cell membrane destruction, depleting the cells of antioxidants or by toxicity from free radical peroxidation products; or through altering signaling pathways, including redox regulation of genes. Morris-Stiff et al.[113] evaluated antioxidant profiles of patients with recurrent acute or chronic pancreatitis and found evidence of multiple antioxidant deficiencies. Zinc status in its relationship to chronic pancreatitis and oxidative stress has also received attention.[114,115] As a result of these and other findings, an emerging therapy in the treatment of pain (that might also arrest the development of chronic pancreatitis in high-risk groups) is the use of micronutrients/antioxidants.[85] The mechanism of pain relief by antioxidants is thought to be mediated through a reduction in oxidative stress and pancreatic inflammation. A recent study from India evaluating daily doses of 600 mcg organic selenium, 0.54 g ascorbic acid, 9000 IU beta-carotene, 270 IU alpha-tocopherol, and 2 g methionine concluded that antioxidant supplementation was effective in relieving abdominal pain in patients with CP.[116] This study has been criticized due to postrandomization dropouts, the high prevalence of tropical pancreatitis in the patient population studied, and hence the generalizability to other patient populations with CP.[117,118] Although some clinicians prescribe antioxidants in practice, larger studies to determine which antioxidants, dose, and length of therapy might be most efficacious, and if there are differences between the treatment effect and the underlying etiology of chronic pancreatitis.

Other interventions include counseling the individual in alcohol and smoking cessation, controlling hypertriglyceridemia by way of glycemic control, or lipid lowering agents as necessary; if hyperparathyroidism is present creating hypercalcemic-induced pancreatitis needs to be brought under control, and eradicating and preventing the further development of gallstones.[119] Control of pain should increase appetite and nutrient intake.

Nutritional Management

Oral Diet

In some patients, modifications of oral intake may reduce abdominal pain and reverse early changes of malnutrition. Although high fat diets are more likely to induce pancreatic enzyme secretion than high carbohydrate diets, there are no randomized trials that have investigated a low fat versus high

fat diet in this patient population; in some, a low fat diet may further accelerate the calorie deficit that often plagues these patients. Still, some clinicians feel this is a worthwhile intervention to control pain, as long as overall nutritional status is monitored. Substituting medium-chain triglyceride (MCT) oil for long-chain fat has been shown to decrease cholecystokinin (CCK) levels and pancreatic stimulation in normal volunteers; it also improved persistent pain in patients with CP.[120] However, the study group was not tried on a standard enteral formulation for comparison. In a small study of patients with severe pancreatic insufficiency, Caliari et al.[121] found that MCT was absorbed better than long-chain triglycerides, but required pancreatic enzymes for optimal absorption. The authors concluded that no advantage is to be expected from replacing usual dietary fats with MCTs if pancreatic supplements are used.[121] In a recent study by Singh et al.,[94] dietary counseling was demonstrated to be as effective as the use of an oral liquid supplement.

Nutrition Support

For the 5% to 15% of patients with a more difficult, refractory disease course, more invasive nutritional therapy may be required. Unlike those with acute pancreatitis based on evidence to date, patients with CP may be tried on gastric feeding first; in those who do not tolerate gastric feedings, the provision of EN through jejunal access should be pursued. The jejunal placement of the feeding tube may be achieved by nasojejunal placement, the nasogastric–jejunal extension tube (NG-J),[122] the conversion of a percutaneous endoscopic gastrostomy (PEG) tube to a percutaneous endoscopic gastrojejunostomy (PEG/J) tube, or by the placement of a direct percutaneous jejunostomy tube (DPEJ). Endoscopic, radiological, and surgical techniques are described for such procedures in Chapter 12. In retrospective studies, the use of prolonged nasojejunal feedings resulted in fewer complications, a lesser need for surgical intervention, and fewer readmissions to the hospital than placement on an oral diet.[123,124] In one case series, long-term enteric feeding through a PEG/J or DPEJ tube over 6 months resulted in a significant reduction in the incidence of abdominal pain (96% to 24%), and in the number of patients requiring narcotic analgesia (91% to 28%).[78] In those with pancreatic insufficiency, pancreatic enzymes may be used with standard products; however, the microspheres make it difficult to administer, and the cost of doing so can increase the financial burden over the use of a semielemental or elemental product (Table 28-11). See Practice Scenario 28-2 for an example of a patient with chronic pancreatitis and malnutrition.

Practice Scenario 28-2

Question: Is this patient a candidate for nutrition support (EN or PN)?

Scenario: A 42-year-old male presented for his sixth admission this year to the hospital with an exacerbation of chronic abdominal pain. The pain was described as a penetrating, deep epigastric pain, radiating to the back, and made worse by eating. The patient had a history of chronic ethanol abuse, and admitted to an episode of binge drinking 1 week before admission. On a review of the systems, the patient complained of soft, runny, "greasy" stools with increased bloating. He reported extreme thirst, frequent urination, nausea, and anorexia since his abdominal pain had worsened. Physical examination revealed a thin Caucasian male appearing older than his stated age. Height was 5'8" and weight was 128 lb (BMI 19.8), down from his original weight of 153 lb 1 year prior. Current laboratory tests for the patient revealed a normal leukocyte count, with a mild elevation in alkaline phosphatase, and a mildly elevated bilirubin. The patient had normal amylase and lipase, most likely due to his calcified pancreas and insufficient functional pancreatic tissue for synthesizing and secreting these enzymes. Repeat glucose levels were >250 mg/dL with a glycated hemoglobin (HbA1c) of 10; diabetes mellitus had not been clinically apparent in this patient until this admission.

Intervention: Jejunal feedings were initiated at a refeeding level early in the hospital admission.

Answer/Rationale: Because of frequent hospitalizations over the past year, his persistent weight loss in the setting of continued oral (gastric) intake, the low likelihood that a male alcoholic will get symptom relief from enzyme supplementation, and the severity of damage to the gland (as evidenced by endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) findings and endocrine and exocrine insufficiency), the patient is a good candidate for jejunal EN.[127] If the patient is cooperative, a trial of nasojejunal feeding at home may provide the opportunity to determine a response to this management strategy. More permanent enteral access would be achieved by DPEJ or PEG/J placement. This procedure may be performed in the outpatient setting and should not be difficult in a thin patient with no previous abdominal scars, surgeries, or ascites. The successful placement of a DPEJ or PEG/J and the initiation of jejunal feeds would be expected to improve nutritional status, increase the likelihood for symptomatic relief, and reduce the frequency for subsequent hospitalizations in the future. This patient is at a significant risk for refeeding syndrome, accelerated in fact, as his hyperglycemia is brought under control.[128] He will need to be started at a refeeding level of calories between 15 to 20 kcal/kg while his glucose is carefully controlled. Electrolytes will need to be carefully monitored and replaced. Ultimately, this patient may need >35 kcal/kg/d to achieve weight gain with good glycemic control and adequate hydration. As current pancreatic enzyme preparations are not able to be used with jejunal feeding tubes without significant clogging potential, the patient will need a semielemental formula, and if unsuccessful due to persistent steatorrhea and failed clinical response, an elemental product.

Pancreatic Insufficiency

Pancreatic enzyme supplementation is a key factor in maximizing absorption in the patient with CP; however, it does not completely abolish steatorrhea.[126] Enzymes typically contain various concentrations of lipase, protease, and amylase. The dose of enzymes usually required to treat steatorrhea should contain the concentration of enzymes that approximates 10%

TABLE 28-11 MCT Containing and Very Low Fat Commercial Enteral Formulas[125]

Enteral Product	Kcal/mL	$ Cost /1500 kcal	Total g fat/ 1500 kcal	MCT/LCT %		MCT:LCT/ 1500 kcal (g)	
Optimental[a]	1.0	36.70	42	28	72	11.9	30.7
Peptamen[b]	1.0	42.48	59	70	30	41	17.5
Peptamen AF[b]	1.2	40.85	68.5	50	50	62.5	62.5
Peptamen 1.5[b]	1.5	36.67	55	70	30	39	16.8
Perative[a]	1.3	13.23	56	40	60	22.4	33.6
Portagen[c](powder)[e]	1.0	19.28	75	87	13	62.2	9.3
Vital HN[a] (powder)	1.0	36.50	16.5	48	52	7.2	7.8
Vital HN 1.5[a]	1.5	30.01	57.1	47	53	26.8	30.3
Vivonex TEN[b] (powder)	1.0	41.65	4.2	n/a	n/a	–	–

[a]Abbott Nutrition: 800-227-5767 or www.abbottnutrition.com
[b]Nestle Nutrition:800-422-2752 or www.nestle-nutrition.com/Public/Default.aspx
[c]Mead Johnson Nutrition: 800-222-9123 or www.meadjohnson.com
[e]Per Mead Johnson: "Portagen powder is not nutritionally complete. If used long term, supplementation of essential fatty acids and ultra-trace minerals should be considered."
Reproduced with permission. McCray, S, Parrish CR. Nutritional Management of Chyle Leaks: An Update. *Practical Gastroenterology.* 2011;XXXV(4):12.

of what the pancreas would normally produce and achieve maximum efficacy at a pH of 7 to 8. Such a dosage is usually accomplished by orally taking (30,000 IU of lipase) per meal.[93] Enteric-coated enzyme preparations resist degradation by gastric acid and are absorbed after passage into the small bowel.

TABLE 28-12 Factors That May Affect the Efficacy of Pancreatic Enzyme Replacement

- Compliance
- Dosing of enzymes (Table 28-13)
- Timing of enzymes
  - Enzymes should be taken with meals, and no more than 30 minutes prior to eating in order to have maximum effectiveness and ideally in smaller amounts throughout meal for best mixing.
  - Needs to be given with snacks also
- Acidic gastric environment
  - Decreased bicarbonate secretion and increased gastric acidity may reduce enzyme activity by delaying the release of enzyme in the proximal duodenum.
  - The enteric coating that protects the digestive enzyme is not dissolved until pH approaches 6.
  - If this does not occur early in the duodenum, it may be helpful to add adjunct therapies such as proton pump inhibitors, H2 blockers, or bicarbonate tablets, all of which help to raise the pH of gastric secretions higher in the duodenum, increasing the efficacy of enzymes.
- Slow gastric emptying
  - Consider prokinetic, if appropriate
- Exposure of enzymes to heat during storage
  - Enzymes stored in an exceptionally hot environment (such as in an automobile during the summer), may lose efficacy.

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If uncoated enzymes were to be used, gastric acid suppression is typically necessary to prevent the inactivation of lipase. Currently, there are no uncoated preparations on the market in the United States. Enteric-coated enzymes were designed to avoid this problem; however, fat malabsorption often persists in CP due to an insufficient bicarbonate secretion needed to neutralize the gastric acidic entering the proximal small bowel unless acid suppression is used.[97] The lipase contained in these enteric-coated products requires a luminal pH of at least >5.0; bile acids will also become deactivated at an acidic pH adding to malabsorption.

TABLE 28-13 Methods Used to Dose Pancreatic Enzymes

- 500–2500 U lipase/kg/meal
- <10,000 U lipase/kg/day
- 1000–4000 U lipase/1 g dietary fat per day at meals and snacks
  - Assessing lipase units per gram of fat in the diet is useful in those situations where the per kilogram enzyme dose appears higher than recommendations, but the diet and symptoms suggest a need for increased lipase.
- Swallow beads without crushing or chewing to maintain the enteric coating
  - Fat malabsorption may persist in CP due to insufficient bicarbonate secretion needed to neutralize acidic stomach contents that enter the proximal small bowel. The lipase contained in enteric-coated products requires a luminal pH of at least >5.0; bile acids will also become deactivated at an acidic pH adding to malabsorption.
- Consider adding to enteral feeding or bolusing in set doses every few hours; also see www.ginutrition.virginia.edu under Resources for the Nutrition Support Clinician.

CP, chronic pancreatitis. Used with permission from the University of Virginia Health System Nutrition Support Traineeship Manual, July 2010.

Nonenteric preparations, if available, should be given with an acid-reducing agent, such as a proton pump inhibitor or an H2 blocker to avoid degradation by gastric acid.[97,129] Enzymes should be taken with meals and snacks, so that the enzymes are timed to be present when the food passes into the small bowel.[97] Poor tolerance of enzyme supplements may occur in some patients, as evidenced by nausea, bloating, cramping, constipation, and diarrhea. Failure to respond to initial enzyme therapy usually is related to noncompliance, inadequate dosing, insufficient acid suppression, or poor timing (Table 28-12). Changing to a different enzyme preparation, increasing the dose, or decreasing the fat in the diet may improve response. Restricting fat in the diet is required only if symptoms (especially weight maintenance, diarrhea, and steatorrhea) are poorly controlled on enzyme therapy or if pain persists on both enzyme supplementation and narcotic analgesia.

The U.S. Food and Drug Administration (FDA) recently determined that pancreatic enzyme supplements currently on the market varied in composition, enzyme activity, formulation, stability, and bioavailability differences leading to variable therapeutic performance. As a result, all preparations were required to undergo new drug applications to demonstrate efficacy by April 28, 2010, or be removed from the marketplace. Table 28-14 provides those pancreatic enzymes that obtained, or have pending FDA approval as of April 21, 2011. For more information see http://www.fda.gov/OHRMS/DOCKETS/98fr/04-9652.htm.

TABLE 28-14 FDA-Approved Pancreatic Enzyme Replacement Therapy[130]

Name	Amylase Units	Lipase Units	Protease Units	Contact
Creon 6000	30,000	6000	19,000	Abbott (Solvay) www.abbottgrowth-us.com (800) 241-1643
Creon 12,000	60,000	12,000	38,000	Abbott (Solvay) www.abbottgrowth-us.com (800) 241-1643
Creon 24,000	120,000	24,000	76,000	Abbott (Solvay) www.abbottgrowth-us.com (800) 241-1643
Pancreaze	n/a	1000	n/a	Ortho-McNeil www.mcneilpediatrics.net (800) 526-7736
Zenpep 5000	27,000	5000	17,000	Eurand www.zenpep.com (800) 716-6507
Zenpep 10,000	55,000	10,000	34,000	Eurand www.zenpep.com (800) 716-6507
Zenpep 15,000	82,000	15,000	51,000	Eurand www.zenpep.com (800) 716-6507
ZenPep 20,000	109,000	20,000	68,000	Eurand www.zenpep.com (800) 716-6507

Pancreatic Enzyme Products **PENDING** FDA approval[a]

- Ultrase Capsules
- Ultrase MT 12 Capsules
- Ultrase MT 18 Capsules
- Ultrase MT 20 Capsules
- Viokase 8 Tablet
- Viokase 16 Tablet

*Contact: Axcan www.axcan.com (800) 950-8085

[a]All are oral, delayed release capsules. Capsules cannot be chewed or crushed. Capsules can be opened and contents sprinkled: (www.epocrates.com) (www.rx-list.com)

Resource: www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204745.htm

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