The purpose of this paper is to outline the historical acquisition of knowledge relevant to the pancreas; to review the evolution of the identification, classification and management of acute pancreatitis; and to comment on the current options and future directions for treatment of acute pancreatitis.

Acute pancreatitis is a term applied to describe a spectrum of inflammatory processes or responses of the pancreatic cell mass, related to a variety of etiologies, that results in the activation of endogenous enzymes and auto-destruction of its tissue (1-4). The clinical presentation of acute pancreatitis can vary from a mild, transient and self-limited disorder, which usually resolves spontaneously with supportive management in four to five days in the vast majority of patients, to a severe form of pancreatitis in 15% to 20% of patients, which is associated with organ failure and multiple local and systemic complications which can be lethal (1-6).

The incidence of pancreatitis in the United States is 30 per 100 000, and in 1999, pancreatitis was the cause of 3 269 deaths, 84% caused by acute pancreatitis and the remaining 16% by chronic pancreatic disease (1, 2, 8). It is estimated that most of the 250 000 patients in the United States diagnosed with acute pancreatitis each year develop the disorder secondary to gallstones or excessive alcohol intake (9).

The time-honored dictum stating that pancreatitis behaves as a benign condition in 80% of patients was confirmed in Italy in 2004 in a study of 1005 patients with a mean age of 59.6 ± 20 years and a male: female ratio of 53:47 (6). The severity of the disease, according to the Atlanta classification, was mild in 75%, and severe in 25% of the patients (6). The etiology was biliary in 60%, alcohol in 8.1%, and indeterminate in 21% of the patients (6).

Multiple reports document an increasing incidence of acute pancreatitis in recent years. In a review of the hospital admissions and the mortality rate related to pancreatitis in England from 1963 to 1998, the incidence of acute pancreatitis was reported to have increased from 4.8 per 100 000 in 1963 to 9.8 per 100 000 in 1998 (3). During the 35-year period of the study, the mortality rate for acute pancreatitis remained relatively stable at approximately 5% (3). Another study from England also reported an increase in the incidence of acute and chronic pancreatitis from 14.5 per 100 000 to 20.7 per 100 000 over the 10-year period between 1990 and 2000 (7).

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The greatest clinical advance in understanding and managing patients with acute pancreatitis in the later half of the 20th century has been the recognition that pancreatitis is not a single disease, but consists of multiple diseases with multiple etiologies, having different natural histories and requiring different treatments (10). A brief review of the history, anatomy and pathophysiology of the pancreas, together with the etiology, classification and diagnosis of acute pancreatitis is offered to facilitate the understanding and rationale of the effective treatment of this challenging disorder.
History

The first description of the pancreas is attributed to Herophilus, a Greek anatomist, in the third century B.C., but it was not until the first century A.D. when Rufus of Ephesus first named this organ the pancreas (Greek pan meaning all, and kreas meaning flesh = pancreas) (2).

Knowledge about the pancreas and pancreatic function did not progress further until the 17th century (1642) when Johann Georg Wirsung described the main pancreatic duct. His discovery opened new fields of study of the pancreas although he never knew its real function (11, 12). In 1720, Abraham Vater described the duodenal ampulla which is named after him, and in 1742, Giovanni Santorini described the accessory pancreatic duct now bearing his name (13). Although others described inflammation of the pancreas from the time of Galen, it was Reginald Huber Fitz, an American physician from Massachusetts who first described acute pancreatitis in the English literature, in his work: “Acute pancreatitis, the consideration of pancreatic hemorrhage, hemorrhagic supplicative, and gangrenous pancreatitis, and of disseminated fat-necrosis”, published in the “Boston Medical and Surgical Journal” in 1889.

Subsequently, Opie, in 1901, proposed his common channel theory of the etiology of acute pancreatitis after he found an impacted gallstone in the papilla in a patient with pancreatitis (11, 14).

The concept of a common channel in the distal common duct which could result in reflux into the pancreatic duct led to the use of sphincterotomy to minimize or prevent reflux as a cause of acute pancreatitis (13). With experience and the passage of time, sphincterotomy became less popular, as the reflux theory of the etiology of acute pancreatitis seemed to be less tenable (13, 15). Thus, the treatment of acute pancreatitis continues to be non-operative and supportive in most patients, with the exception of those with necrotizing pancreatitis.

Elman et al. (11, 16) in 1929, were the first to describe the association of hyperamylasemia with acute pancreatitis. Since then, clinical determination of the serum amylase level has remained a valuable tool that has been used as a mainstay for the diagnosis of this disease. In 1936, Lim and his Chinese colleagues first described the qualitative relationship between the basic components and the other compounds of pancreatic secretion (10, 17). This led to the discovery, by Hollander and Birnbaum in 1952, of the participation of the ductal system in pancreatic secretion, primarily of water and bicarbonate, and the role of carbonic anhydrase in the pancreatic secretory process (18). One of the most decisive, fundamental contributions to the knowledge of pancreatic function, both physiological as well as pathophysiological, was made by George Palade with his Nobel Prize winning work in 1974 on the synthesis and excretion of proteins by the exocrine cells of the pancreas. He described the biochemical steps in pancreatic enzyme synthesis, segregation, transport, storage and secretion, together with the ultrastructural intracellular units related to each process (10, 19-22). In 1968, Douglas introduced the concept of stimulus-secretion coupling to describe the process involved in both the ductal and the acinar cells in the intracellular regulation of secretions (10, 23). Several investigators subsequently developed the concept of cellular receptors for various hormones and chemical stimuli, which was surveyed and put into the perspective of pancreatic secretion in 1986 by Gardner and Jensen by their description of the receptors mediating the actions of secretagogues on pancreatic acinar cells.

In 1975, Petersen described electrical coupling between the pancreatic acinar cells, and in 1980 published a report of his studies of the stimulation of adjacent cells by the passage of inorganic ions and other substances from one cell to another through intercellular channels (10, 24). By the closing years of the 20th century, development of molecular biology and discovery of gene expression in the exocrine pancreas opened opportunities for expansive investigation not only of the pancreas, but for the exploration of biological phenomena and function to a greater depth and with broader scientific horizons than ever before possible (10, 26).

From a valuable, practical clinical aspect of the field, Ranson et al., in 1974, described criteria associated with poor prognosis for patients with acute pancreatitis (1, 2, 27). Ranson’s criteria, which consider the status of 11 clinical findings within 48 hours of the onset of acute pancreatitis, continue to have merit.
clinically in predicting the severity of acute pancreatitis (tab. 1). If three or more of Ranson’s criteria are manifested within 48 hours of onset of symptoms, severe acute pancreatitis is suggested. In patients with only one or two criteria, the predicted mortality of acute pancreatitis is 1%, which increases to 10% in patients with three criteria, and to 50% in patients with seven or more criteria. The major limitations of Ranson’s criteria are that comprehensive assessment of the patient requires data that may not be available until after 48 hours following admission, and that the criteria cannot be calculated serially for valid assessment later during the hospitalization (9).

Pancreatic physiology (29), pathophysiology and acute pancreatitis

The pancreas is a compound gland responsible for multiple physiologic functions accomplished by its endocrine secretion of hormones by the islet cells, its exocrine secretion of digestive enzymes by the acinar cells, and large volumes of sodium bicarbonate ions and water secreted mainly by the epithelial cells of the small ductules arising from the acini. Although acetylcholine released from parasympathetic endings and other cholinergic nerves in the intestine can initiate pancreatic secretions, especially the acinar cells, pancreatic secretions are stimulated primarily in response to chyme in the upper small intestine, and the characteristics of the secretions are determined to some extent by the types of food substances in the chyme. Acid chyme from the stomach, having a pH less than 4.5 as it enters the duodenum, releases and activates secretin, which in turn causes the ductal endothelial cells to produce copious volumes (about 1000 ml daily) of pancreatic fluid containing high concentrations of bicarbonate ions. The bicarbonate laden fluid neutralizes the gastric acid and provides a slightly alkaline medium in the duodenum and upper jejunum, which is optimal for the action of the pancreatic enzymes secreted in response to cholecystokinin release from the duodenum.

Products of partial protein digestion such as proteoses and peptides, together with long chain fatty acids and hydrochloric acid, are the main stimuli for cholecystokinin release and its subsequent stimulation of acinar cell enzymes. The proteolytic enzymes include trypsin, chymotrypsin, carboxypolypeptidase, ribonuclease and deoxyribonuclease. Trypsin, the most abundant of these enzymes, and chymotrypsin cleave the intact and partially digested proteins into various peptides, but do not split them further to individual amino acids. Carboxypolypeptidase cleaves individual amino acids from the carboxyl ends of the peptides, thus completing digestion of the proteins to their fundamental amino acid components. The action of the two nucleases is to cleave ribonucleic and deoxyribonucleic acids. In the digestive process for carbohydrates, pancreatic amylase hydrolyzes starch, glycogen and most other carbohydrates, except cellulose, to disaccharides and trisaccharides. In the digestion of fat, pancreatic lipase hydrolyzes neutral fat to fatty acids and monoglycerides, while cholesterol esterase hydrolyzes cholesterol esters, and phospholipase cleaves fatty acids from phospholipids.

Proteolytic enzymes are synthesized in the acinar cells as trypsinoen, chymotrypsinogen, and procarboxypolypeptidase, which are inactive biologically. Ordinarily, these enzyme precursors are activated, only after secretion into the duodenum, by enterokinase, an enzyme secreted by the intestinal mucosa when it is stimulated by chyme. These enzyme precursors, also known as proenzymes or zymogens, can also be activated autocatalytically by trypsin that has already been formed (1, 2, 29, 30).

Obviously, it is essential that the proteolytic enzymes produced by the pancreas under normal conditions are not activated until they reach the intestine. Otherwise, the trypsin and other enzymes would autodigest the pancreas. To prevent this possibility, the same cells that

<table>
<thead>
<tr>
<th>Ranson’s criteria</th>
<th>Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt; 55 years</td>
</tr>
<tr>
<td>Leucocytosis</td>
<td>&gt; 16 000</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>&gt;200 mg/dL</td>
</tr>
<tr>
<td>LDH</td>
<td>&gt;350 IU/L</td>
</tr>
<tr>
<td>AST/(SGOT)</td>
<td>&gt;250 U/dL</td>
</tr>
<tr>
<td>First 48 hours</td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td>&gt;5 mg/dL</td>
</tr>
<tr>
<td>PaO₂</td>
<td>&lt;60 mm Hg</td>
</tr>
<tr>
<td>Calcium</td>
<td>&lt;8 mg/dL</td>
</tr>
<tr>
<td>Base deficit</td>
<td>&gt;4 mEq/L</td>
</tr>
<tr>
<td>Fluid sequestration</td>
<td>&gt; 6 l</td>
</tr>
<tr>
<td>Decrease Hct</td>
<td>&gt;10%</td>
</tr>
</tbody>
</table>
secrete the proteolytic enzymes simultaneously secrete trypsin inhibitor. Trypsin inhibitor surrounds the zymogen granules within the cytoplasm of the acinar cells, thus preventing activation of trypsin both inside the cells and in the acini and ducts of the pancreas. Because it is trypsin that triggers the activation of the other proteolytic enzymes, trypsin inhibitor ultimately prevents activation of all of the proteolytic enzymes. To summarize, factors exist under physiologic conditions to protect the acinar cells, and to prevent the activation of pancreatic enzymes within the pancreatic cellular and ductal system and thus to avoid pancreatic inflammation and autodigestion.

These include the following:

1) enzyme precursors are secreted as proenzymes or zymogens that ordinarily require intraluminal intestinal activation, usually initiated by enterokinase;

2) the proenzymes are produced in the acinar cells and transported in the acini and ducts surrounded by membrane bound organelles (zymogen granules) to prevent their activation;

3) pancreatic trypsin inhibitor is also produced and is present to prevent activation of the proenzymes in the pancreatic ducts (30). However, these protective mechanisms can be overcome in acute pancreatitis. If the parenchyma of the pancreas becomes damaged, or if a pancreatic duct is blocked, pancreatic secretions can become pooled in the damaged areas of the pancreas. The trypsin inhibitor can subsequently be overwhelmed, and the pancreatic proenzymes can be rapidly activated and begin to digest the substance of the pancreas itself, resulting in acute pancreatitis. Early activation of trypsin has been shown experimentally to be one of the precipitating pathologic events in acute pancreatitis related to early activation of enzymes (30). Once this occurs, the trypsin activates even more trypsinogen, as well as chymotrypsinogen and carboxyprotease, which results in a vicious cycle until most of the proteolytic enzymes in the pancreatic duct and acini become activated. These enzymes rapidly digest large portions of the pancreas itself, sometimes completely and permanently destroying the ability of the pancreas to secrete digestive enzymes (29).

Ordinarily, the islet cells of the pancreas are not seriously affected by acute pancreatitis so that insulin continues to be secreted by the endocrine pancreas, even though the secretions of the exocrine pancreas are markedly reduced (29). Cathepsin-B, a lysosomal cystein protease in the acinar cells, has been studied, and it has been shown to stimulate the conversion of trypsinogen to trypsin directly. Moreover, its complete inhibition blocks 90% of the conversion of trypsinogen to trypsin (1, 2, 30, 31).

Cathepsin-B also strongly activates mesotrypsinogen, one of the pancreatic isoforms of trypsinogen. The function of mesotrypsinogen appears to be related to the inactivation of pancreatic secretory trypsin inhibitor, thus preventing the degradation of activated trypsin in the acinar cell lumen (30). The next result of the actions of Cathepsin-B appears to be preservation of the trypsin cascade both by active stimulation of its formation and by neutralization of inhibitors of its productions and activity.

The final event is the activation of other enzymes like chymotrypsin, elastase, and carboxyprotease, which cause autodigestion of the pancreatic tissue. The local tissue inflammation stimulates activation of cytokines, especially Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-10 (IL-10) and Tumor Necrosis Factor (TNF) that account for the systemic effects related to pancreatitis (1, 2, 4, 30-33).

Etiology of acute pancreatitis

Many conditions have been associated with the etiology of acute pancreatitis, however, up to 80% of the cases are related to biliary stones or to excessive alcohol consumption. The incidence of these two principal etiologic factors in the development of acute pancreatitis vary throughout the world, related to diet, cultural behavior and genetic factors (tab. 2).

<table>
<thead>
<tr>
<th>Etiologies of acute pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Biliary tract stones</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Parasites</td>
</tr>
<tr>
<td>Medications, drugs</td>
</tr>
<tr>
<td>Tumors</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Osteoperative</td>
</tr>
<tr>
<td>Post ERCP</td>
</tr>
<tr>
<td>Scorpion sting</td>
</tr>
</tbody>
</table>
**Biliary stones**

Biliary stones are among the most common etiologic conditions related to the development of acute pancreatitis, and this association has been recognized for more than 100 years since the pioneering work of Opie in 1901 in which he proposed a common channel, common duct reflux theory (14). However, the pathophysiology of this process is not fully understood, and, furthermore, cannot be implicated as the etiology of the vast majority of cases of acute pancreatitis. Some theories have proposed a purely mechanical obstructive event as the etiology for acute pancreatitis (1, 2, 4, 5). Credence for this mechanism is favored by reports of gallstones recovered from the stool in 90% of patients studied with biliary pancreatitis (12). Nonetheless, only 2% of patients with acute pancreatitis have been found to have a stone impacted in the ampulla of Vater.

**Alcohol**

Alcohol intake has been associated with pancreatitis, but the ultimate pathophysiologic or pathobiochemical explanation for this association is not completely clear. The incidence of acute pancreatitis related to alcohol consumption is growing in industrialized countries, and appears to be related to the increasing availability and consumption of alcoholic beverages and with the increasing social acceptance of alcohol dependency and abuse (1, 2, 4, 34). Animal studies have shown that alcohol increases the sensitivity of the pancreas to zymogen activation and subsequent pancreatitis (34). Another effect of alcohol on the pancreas is to increase vagal stimulation of pancreatic secretion as well as to induce an increase in the tone of the sphincter of Oddi, which favors pancreatic ductal hypertension and development of pancreatitis (2, 4, 34, 35).

**Dyslipidemia**

Dyslipidemia type I and type V have been implicated as etiologies of pancreatitis. The pathophysiologic effects appear to be related to the liberation of free fatty acids by lipase in the microcirculation of the pancreas, and the subsequent secondary activation of enzymes in the acinar cells (1, 4).

**Iatrogenic**

Acute pancreatitis has also occurred in relation to procedures performed directly on the pancreas or its drainage system as well as to procedures that produce hypothermia or low perfusion states. One of the common causes of iatrogenic pancreatitis is endoscopic retrograde cholangiopancreatography (ERCP) with a reported incidence of 3% to 4%. Biliary tract exploration can also precipitate acute pancreatitis in 0.5% to 3% of patients (1, 2, 4).

**Medications**

Many reports of medication-related pancreatitis have been published, but this association is difficult to establish because many medications can cause non-pancreatitis related hyperamylasemia. However, some medications have been clearly implicated as a cause of acute pancreatitis (tab. 3) (1, 2, 4, 5).

**Trauma**

Blunt trauma to the abdomen may result in crush injury to the pancreatic tissue, which may produce acute pancreatitis, or which may eventually result in strictures of the pancreatic duct that can lead to pancreatitis in the future.

**Hypercalcemia**

The precipitation of calcium crystals in the pancreatic duct in patients with hypercalcemia can induce pancreatitis (1, 4).

**Infections**

Viral infectious diseases such as cytomegalovirus, measles, and Coxsackie infections have been reputed to cause acute pancreatitis. Parasitic infections such as Ascaris lumbricoides and Clonorchis sinensis can cause pancreatitis as a result of their obstructing the biliary tree. Tuberculosis has also been implicated as a cause of acute pancreatitis (1, 4).

**Tumors**

Tumors of the head of the pancreas or periampullary tumors can be the etiology of pancreatitis in 1% to 2% of patients with neoplasms in these areas (1, 2).

### Table 3. Medications related to etiology of acute pancreatitis

<table>
<thead>
<tr>
<th>Strong association</th>
<th>Probable association</th>
</tr>
</thead>
<tbody>
<tr>
<td>sulfonamides</td>
<td>acetaminophen</td>
</tr>
<tr>
<td>salicylates</td>
<td>cimetidine</td>
</tr>
<tr>
<td>didanosine</td>
<td>methyllydopa</td>
</tr>
<tr>
<td>estrogens</td>
<td>sulindac</td>
</tr>
<tr>
<td>metronidazole</td>
<td>isoniazid</td>
</tr>
<tr>
<td>furosemide</td>
<td>clozapine</td>
</tr>
<tr>
<td>mercaptopurine</td>
<td>zalcitabine</td>
</tr>
<tr>
<td>pentamidine</td>
<td>phenformin</td>
</tr>
<tr>
<td>azathioprine</td>
<td>corticosteroids</td>
</tr>
<tr>
<td>tetracyclines</td>
<td>warfarin</td>
</tr>
<tr>
<td>thiazides</td>
<td>asparaginase</td>
</tr>
<tr>
<td>valproic acid</td>
<td>procainamide</td>
</tr>
</tbody>
</table>
Idiopathic

The precise inciting events of some episodes of acute pancreatitis have not been identified and, therefore, the etiology in such cases is considered idiopathic.

Classification

The classification of pancreatitis has changed in accordance with the progress in knowledge of the disease as well as with the changes in the available diagnostic technology. The first attempt to achieve a comprehensive classification occurred at the Symposium on the Classification of Pancreatitis in Marseilles in 1963, where a clinicopathologic classification was favored. Pancreatitis could be classified as acute, acute relapsing, chronic, and chronic relapsing. This classification was reviewed with minor changes to add subclassifications for pancreatitis during the second Marseilles Symposium in 1984 (36).

From the International Symposium on Acute Pancreatitis in Atlanta, Georgia in 1992, a new classification arose, which focused on the clinical findings of the patients, but at the same time, was simple and clear enough to permit adequate comparisons among various clinicians and their outcomes (37) (tab. 4). The Atlanta Classification identifies patients as having severe pancreatitis if they meet one of the following criteria (32, 37):

- organ failure with systolic blood pressure <90 mm Hg, PaO₂ <60 mm Hg, creatinine > 2 mg/dL, or gastrointestinal tract bleeding >500 mL over 24 hours,
- local complications such as necrosis, pseudocyst or infected collection,
- three or more Ranson’s criteria,
- 12 or more points in the APACHE II classification.

A clinically based classification system for acute pancreatitis

In 1974, Ranson et al reported a severity score, based on physiological parameters, measured at admission and at the first 48 hours of disease presentation (27, 32, 37) (tab. 1). This has been discussed in the history section.

Balthazar described a classification according to the findings on CT scan (tab. 5).

He correlated the severity of the changes encountered on CT scan with the morbidity and mortality rates. Patients with no abnormalities on CT scan are classified as Grade A with a morbidity and mortality of 4% and zero, re-

Table 4. Atlanta classification

Acute pancreatitis: an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems.

<table>
<thead>
<tr>
<th>CT Grade</th>
<th>Points</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>3</td>
<td>54%</td>
<td>14%</td>
</tr>
<tr>
<td>E</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>2</td>
<td>48%</td>
<td>0%</td>
</tr>
<tr>
<td>30-50%</td>
<td>4</td>
<td>75-100%</td>
<td>11-25%</td>
</tr>
</tbody>
</table>

Mild acute pancreatitis: associated with minimal organ dysfunction and an uneventful recovery, without the described features for severe pancreatitis.

Severe acute pancreatitis: pancreatitis associated with organ failure, and/or local complications, such as necrosis, abscess, or pseudocyst.

Acute fluid collections: fluid collections that occur early in acute pancreatitis, located in or near the pancreas, and lacking a wall of granulation or fibrous tissue.

Pancreatic necrosis: diffuse or focal area(s) of nonviable pancreatic parenchyma, typically associated with peripancreatic fat necrosis.

Acute pseudocyst: a collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue, which arises as a consequence of acute pancreatitis, pancreatic trauma, or chronic pancreatitis.

Pancreatic abscess: a circumscribed intra-abdominal collection of pus, usually in proximity to the pancreas, containing little or no pancreatic necrosis, which arises as a consequence of acute pancreatitis or pancreatic trauma.
be present, and respirations can be shallow secondary to upper abdominal peritoneal irritation. The abdomen, in mild forms of the disease, may be minimally tender, with normal or mildly decreased bowel sounds. As the severity of the disease increases, the abdominal examination can be more impressive, with guarding, rebound, gastric distension, and absence of bowel sounds.

Hemorrhagic complications occur in about 1% of patients with acute pancreatitis. They may present with ecchymotic discolorations of the flanks (Grey Turner’s sign) or periumbilical discoloration (Cullen’s sign) that represent retroperitoneal hemorrhage or hemorrhage into the falciform ligament, respectively (1, 2, 5). Patients with more severe forms of the disease may present with shock, acute respiratory distress syndrome, alterations of mental status, or even coma.

General markers

The complete blood count (CBC) is an important tool in the evaluation of acute pancreatitis. Although not a specific or particularly sensitive marker for the diagnosis of pancreatic inflammation, it is used to help determine the intensity of the attack. Severity scores such as those of Ranson or Imrie utilize an elevated leukocyte count, usually above 15 000 as one of their criteria (1, 2, 5, 27, 32, 42). In addition, other indices such as the hemoglobin and hematocrit can be useful in evaluating general clinical status, including dehydration or hemorrhagic complications, which can be suggested by an elevated hematocrit. Moreover, hemorrhagic pancreatitis can be associated with decreasing hemoglobin and hematocrit levels, and serial determinations can be helpful in management.

The BUN and creatinine are useful in the initial evaluation of a patient with pancreatitis; they may indicate intravascular depletion; and they also can be used as prognostic markers, indicating an increase in fluid sequestration (third spacing) in severe cases of pancreatitis (2, 27, 32).

**Table 5. Balthazar classification**

<table>
<thead>
<tr>
<th>CT findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>A  normal pancreas</td>
</tr>
<tr>
<td>B  pancreatic enlargement</td>
</tr>
<tr>
<td>C  pancreatic inflammation or peripancreatic fat</td>
</tr>
<tr>
<td>D  single peripancreatic fluid collection</td>
</tr>
<tr>
<td>E  two or more fluid collections and/or retroperitoneal air</td>
</tr>
</tbody>
</table>

**Table 6. Computed tomography (CT) severity index**

<table>
<thead>
<tr>
<th>Points</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>2-3</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>4-6</td>
<td>36%</td>
<td>6%</td>
</tr>
<tr>
<td>7-10</td>
<td>92%</td>
<td>17%</td>
</tr>
</tbody>
</table>

respectively. On the other hand, patients with two or more collections, or with retroperitoneal air, have a morbidity and mortality of 14% and 14%, respectively. To this classification, Balthazar later added the estimated percentage of pancreatic necrosis, thereby obtaining a combined score known as the acute pancreatitis CT severity index (tab. 6). Patients with Grade E pancreatitis with more than 50% necrosis have an Index of 10 with a morbidity and mortality of 92% and 17%, respectively (4, 38, 39).

Multiple physiologic indexes have been used to predict the severity of pancreatitis. Among them, the APACHE II (Acute Physiology, Age and Chronic Health Evaluation) is one of the more widely used injury severity scores, especially in the intensive care unit setting, and more than 12 points on the APACHE II score indicate severe disease (4, 40, 41).

**Diagnosis**

**Clinical**

Acute pancreatitis has multiple clinical manifestations, and some of its features can lead to its clinical diagnosis, however, biochemical confirmation of clinical manifestations is required to establish the diagnosis (1, 2, 5). The most common symptoms of pancreatitis include: upper abdominal pain, usually in the mid-epigastrium, which can be constricting, radiating to the back, constant and usually persistent for more than a few hours. The pain can be stabbing and may have a sudden, acute onset. Feeding may intensify or aggravate the pain, and leaning forward may improve it. The pain may be associated with nausea and vomiting in a high percentage of patients (1, 2). Patients with biliary-induced pancreatitis may experience biliary colic as a sentinel event.

Physical examination findings vary according to the severity of the attack. The patients are usually restless, trying to find a comfortable position. Fever, tachycardia and diaphoresis are encountered commonly. Tachypnea may...
C-reactive protein (CRP) is an acute phase reactant produced by the hepatocytes and is commonly used as a biochemical indicator of the severity of pancreatitis (2, 43). The elevation in CRP is usually evident in severe pancreatitis by the second to fourth days of symptoms, and although the accuracy can be 0.84, it is a late event in the management of patients. Levels above 120 mg/L are indicative of severe disease (43).

Liver function tests are especially useful in the determination of the etiology of pancreatitis. Elevations in serum bilirubin and transaminases may indicate that the pancreatitis has a biliary etiology. The Blamey criteria for biliary pancreatitis can predict that the etiology of pancreatitis is biliary with 86% accuracy in patients having three criteria and with 95% accuracy in patients having four criteria (1, 44, 45) (tab. 7).

Cytokines are also useful in the evaluation of pancreatitis, especially as predictors or markers of severity. The IL-6 level has shown good correlation with the clinical course of the disease, and the IL-10 level is a good prognostic indicator during early stages of the acute episode (1, 2, 31, 33).

Specific markers

Amylase is a digestive enzyme that has many isoforms, and p-amylase is specific for amylase of pancreatic origin. Serum amylase is usually elevated 2 to 4 hours after the initial manifestation of symptoms and remains elevated for 3 to 6 days. The sensitivity and specificity of hyperamylasemia vary according to the serum amylase level regarded as significant in each institution and the time of the evaluation, with a usual sensitivity of 60% to 95% and a specificity of 80% to 95% (1, 2, 4, 46, 47). Persistent elevation of serum amylase may indicate ongoing inflammation or the development of complications. On the other hand, a normal serum amylase level cannot rule out pancreatitis. Many other diseases can produce elevations of the serum amylase, among them burns, diabetic ketoacidosis, pregnancy, renal failure, perforated ulcer and small bowel injury (2, 46, 47). Urinary amylase levels are used as confirmation for the diagnosis of pancreatitis, especially because the amylase levels are elevated for a longer time in the urine than in serum (2).

Serum lipase is another specific marker of pancreatitis that also rises in acute pancreatitis and remains elevated for a longer time than the serum amylase (1, 2, 5). The specificity of serum lipase in the diagnosis of pancreatitis is between 85% and 100% (1, 5). However, other conditions such as ischemia may cause a non-significant elevation of serum lipase.

Finally, carboxypeptidase B, a 95 amino acid peptide, has been shown to be useful in the diagnosis of acute pancreatitis with a sensitivity and specificity similar to those of serum amylase and lipase (48).

Imaging

The three-view abdominal X-ray series can be used as an initial diagnostic test in the evaluation of patients with abdominal pain. There are no specific routine X-ray images that can establish the diagnosis of pancreatitis, however, other reasons for the symptoms can be ruled out.

Abdominal ultrasonography is useful in the diagnosis of pancreatitis, especially because it can demonstrate gallstones and acute cholecystitis that are associated with biliary pancreatitis. Another useful finding is dilatation of the common bile duct that can be present secondary to choledocholithiasis (1, 2, 4). However, direct visualization of the pancreas is difficult to accomplish with ultrasonography.

The computed tomography (CT) scan has been established as one of the most sensitive and specific tests in the diagnosis of acute pancreatitis and its complications. Balthazar has proposed a classification of the CT scan findings for the diagnosis and prognosis of the acute attack of pancreatitis (tab. 5, 6) (1, 2, 38, 39).

Magnetic resonance (MR) imaging has a high sensitivity for the diagnosis of pancreatitis, but its main use is in outlining the biliary anatomy (2, 49). Multiple reports have also extolled the high accuracy of MR imaging for the demonstration of common bile duct stones (2, 49, 50). The use of secretin may provide additional help in outlining the anatomy of the pancreatic duct (50, 51). These advances in

| Table 7. Blamey criteria for biliary pancreatitis |
|-----------------------|----------------|
| Age                   | >55 years      |
| Sex                   | female         |
| Bilirubin             | >1.5 mg/dL     |
| Amylase               | >4,000 U/L     |
| Alk phos              | >300 U/L       |
| SGPT or SGOT          | >100 U/L       |
technology may limit the need for invasive procedures such as ERCP when common bile duct stones are suspected.

Treatment

**General measures** (fig. 1)

As stated earlier, acute pancreatitis can be a mild and self-limited disease, often requiring no specific treatment (1, 2, 6, 52, 53). The mainstay of treatment for pancreatitis continues to be supportive (1, 2, 6, 52, 53). The first step in the management of acute pancreatitis is early recognition of the clinical scenario and then to determine the severity of the disease using established predictors, including those of Ranson, Imrie, and Balthazar. When etiologic factors are identified, such as medications, hypercalcemia or other offending factors, the first step in the management of these patients is to try to correct the abnormal precipitating clinical situation (1, 2).

Initial measures include adequate hydration of the patient, and crystalloids should be used to achieve an euvolemic state (1, 2, 6, 32, 52, 53). The vital signs and the urine output should be monitored closely because they may reflect dehydration or worsening of the systemic inflammatory response. In patients with more severe forms of the disease, invasive monitoring may be necessary to provide aggressive resuscitation of intravascular volume. Low urine output may be an indicator of severe dise-
ase and should be corrected. The patient’s oxygenation must be supported, and one should be aware of the high risk of developing acute respiratory distress syndrome (ARDS). Some patients may even require artificial ventilatory support for a period of time. Prophylaxis against deep venous thrombosis should also be instituted in all of these patients.

Gastric suction via a nasogastric tube has historically been considered one of the pillars of the treatment of all patients with acute pancreatitis. However, some reports recently have suggested that gastric suction should be limited for use only in patients with persistent gastric distention or refractory vomiting (1, 52, 54). Medications that decrease the acidity of the stomach should be used in patients with acute pancreatitis to prevent gastrointestinal bleeding. H2 receptor blockers and proton pump inhibitors are the most effective medications to decrease acid production and to avoid its secondary complications (1, 2, 6).

Pain control
The classical teaching to avoid the use of morphine as an analgesic in patients with acute pancreatitis has been re-evaluated. In 1937, some reports suggested an increase in the tone of the sphincter of Oddi with morphine administration in animal models (55, 56). However, no randomized trials or human studies support these findings (56, 57). Nonetheless, for many years, the standard practice in treating the pain associated with pancreatitis has been to use meperidine as an analgesic (56, 58). A recent report in the literature questioned this old paradigm, showing that the elevation of the pressure in the sphincter of Oddi is encountered with all narcotics and was even higher with meperidine than with morphine. Furthermore, meperidine is associated with neuro-toxicity (56, 58). Currently, no credible evidence exists to contraindicate the use of morphine in treating the pain associated with acute pancreatitis (56, 58). Finally, the use of effective epidural anesthesia to relieve pain in patients with severe pancreatitis without increasing morbidity has been reported (59).

Antibiotics
Clinical studies have addressed the validity of prophylactic antibiotic use in patients with pancreatitis, and in a series of studies reported in 1975, no favorable effects were found with the use of prophylactic antibiotics in patients with acute pancreatitis (42, 60, 61). However, these studies where done before the era of the CT scan. Subsequently, in 1993, a randomized trial using imipenem versus placebo in patients with necrotizing pancreatitis showed a significant decrease in the incidence of pancreatic sepsis, although a significant reduction in mortality was not obtained (63, 64). Nonetheless, the results of this study recommended the prophylactic use of imipenem in patients with acute necrotizing pancreatitis and has changed clinical practice in some institutions since that time (64). A study reported in 1994 contributed to the knowledge base of the antibiotic treatment for pancreatitis (65). Samples from 12 patients with severe acute pancreatitis were obtained from blood and from pancreatic tissue, confirming that pefloxacin, metronidazole, imipenem and mezlocillin have adequate penetration and achieve therapeutic concentrations in necrotic pancreatic tissue, indicating their effectiveness in patients with infected pancreatitis (65).

Other multicentric studies conducted between 1996 and 2001 suggested improvement in the incidence of infectious complications and in the mortality of patients with necrotizing pancreatitis who were treated with prophylactic antibiotics (66, 67, 68). However, the methodology of these studies has been criticized, and the results have been questioned (52, 64).

In attempting to solve the methodologic problems of previous studies, another group of investigators published their randomized double blind study in 2004, comparing ciprofloxacin plus metronidazole versus placebo in 200 patients with necrotizing pancreatitis as verified by CT scan and/or C-reactive protein greater than 150 mg/L (60). Their recruitment of patients into the study was terminated early because an interim analysis of the antibiotic treatment limb did not show any benefit over placebo (64, 69). Overall, no role is evident for antibiotics in patients with mild acute pancreatitis, but although the evidence is not clear, the use of antibiotics is recommended in patients with infected necrotizing pancreatitis (1, 2, 52, 53, 64). Antibiotic treatment is considered prudent in patients with infected necrotizing pancreatitis or with pancreatic abscess. The antibiotic of choice is imipenem, but metronidazole and fluoroquinolones may be used in patients with allergy or adverse reactions to imipenem; and more specific choices of antibiotic therapy should be guided by culture and
sensitivity results. Additional, well-designed studies are needed to elucidate clearly the role of prophylactic antibiotics in acute severe pancreatitis.

Selective gastric decontamination is another relatively recent strategy that can be followed to manage patients with severe acute pancreatitis. Animal models of pancreatitis showed a decrease in the incidence of pancreatic infection after gastric decontamination with oral antibiotics (1, 2, 6, 70, 71, 72). In 1995, a prospective randomized trial showed a 50% reduction in infectious complications in patients treated with oral gastrointestinal decontamination. However, the concomitant use of intravenous antibiotics in the treatment group has raised many questions regarding the results and conclusions (64, 71).

**Nutrition**

Acute pancreatitis creates a hypermetabolic state, and comprehensive metabolic support is required regardless of the severity of the disease and the co-morbidities of the patient (1, 73, 74). In patients with mild to moderate pancreatitis, gastrointestinal rest with adequate fluid resuscitation is usually sufficient initial management. The oral route for feeding should be re-established as soon as the nausea subsides, and provided that the pain does not reappear upon feeding (1, 2, 6, 52, 53, 73, 74, 75).

Severe pancreatitis is a much more complicated problem. As reviewed previously, the pathophysiologic events in acute pancreatitis are initiated and perpetuated by failure of the control of the state of activation of the pancreatic enzymes in the acinar cell and ductal lumen. Some studies have demonstrated that gastric or duodenal feeding increases the production of enzymes by the pancreas, which may further stimulate or aggravate the disease process and cause more complications (1, 2, 30, 31, 74).

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Before the development of parenteral nutrition and its introduction as a practical clinical tool, patients with severe pancreatitis were often necessarily starved. With the successful clinical application of parenteral nutrition, patients with severe pancreatitis are now able to receive early nutritional support as one of the fundamental adjuncts in the treatment of this disease. Feeding the patient by vein promotes bowel rest and allows the patient time for recovery while providing the metabolic substrates essential to maintain body homeostasis and to restore pancreatic integrity and function to normal.

Recent studies of the physiology of the gastrointestinal tract have demonstrated benefits of enteral feeding especially related to its trophic effects on the intestinal tract (53, 74, 76, 77).

These data have been extrapolated to justify the use of enteral feeding in patients with severe pancreatitis whenever possible. However, enteral feeding should only be attempted in patients with mild or resolving pancreatitis in whom luminal nutrients can be tolerated without untoward pain, vomiting or recrudescence of the process. It is a well established fact that the strongest stimulation of pancreatic exocrine and endocrine secretion is food in the stomach, duodenum and the first meter of the jejunum.

Accordingly, use of a jejunal tube to start enteral feeding in patients with severe pancreatitis can be attempted only cautiously when the ileus resolves and the condition of the patient allows this intervention (53, 74, 78, 79). Moreover, it is strongly recommended that enteral feeding be accomplished by a tube with its tip one meter distal to the ligament of Treitz (73, 75).

**Protease inhibitors**

The use of protease inhibitors such as gabexate mesilate and aprotinin have been proposed in the treatment of severe pancreatitis. The hypothetical mechanism for the effectiveness of these agents is the inhibition of trypsin and, therefore, the amelioration of the activation of the pancreatic enzymes (2, 11, 79, 80). Some of the studies which have been conducted since the 1960’s, have supported the use of these compounds in the treatment of acute pancreatitis.

Studies regarding the prophylactic use of gabexate mesilate or somatostatin in patients who undergo ERCP deserve special mention, since some of them have shown a significant reduction in the incidence of post-procedure pancreatitis (49, 80). However, a recent, better controlled study showed an increased incidence in pancreatitis in the patients treated with prophylactic protease inhibitors, emphasizing once again the lack of consistent information and justification for the use of protease inhibitors in this subgroup of patients (81). This group of investigators published the results of the-
Surgical treatment

**Endoscopy**

Endoscopic retrograde cholangiopancreatography was developed in the 1970’s and initially had a prominent diagnostic role in the demonstration and documentation of biliary pancreatitis. With the development of new technologies, the therapeutic value of this procedure subsequently was also recognized, especially the ability to perform sphincterotomies with the consequent drainage and relief of the biliary obstruction (1, 2, 6, 52, 53). The principal role of endoscopic management of pancreatitis related to biliary obstruction can be therapeutic in patients who experience an acute attack of pancreatitis with the following findings (52, 81, 82, 83):

- ascending cholangitis,
- jaundice,
- dilated common bile duct,
- severe gallstone pancreatitis.

The current recommendation is to perform the ERCP procedure within the first 72 hours after the onset of symptoms (1, 52, 53).

**Cholecystectomy**

In 1742, Petit was the first to perform a successful drainage for empyema of the gall-bladder, starting with the use of local irritants in the peritoneum to accomplish visceral/parietal peritoneal fusion, followed by drainage of the gallbladder with a tube (84, 85, 86). More than a century later, in 1867, John Strough Bobbs in Indianapolis performed an incidental cholecystostomy during celiotomy for ovarian disease (84). In 1882, Langenbuch, a German surgeon, performed the first successful prospective cholecystectomy, a procedure that became the standard for the treatment of gallbladder disease. However, in his original series, the mortality was about 20%. Minor technical modifications to this procedure were made during the 20th century, including the introduction of the cholangiogram by Mirizzi for the evaluation of common bile duct stones. Muhe in Germany and Mouret in France performed the initial laparoscopic cholecystectomies, although Mouret was the first to promote and popularize its use (84-87). By 1992, it was recognized in the United States that the use of laparoscopic cholecystectomy was rapidly becoming the treatment of choice for symptomatic biliary disease (90). In patients with biliary pancreatitis, the current recommended standard of care is that laparoscopic cholecystectomy should be performed after the signs of severe inflammation disappear and before the patient is discharged home (1, 2, 6, 52, 53).

**Imaging guided drainage**

The role of imaging guided drainage in acute pancreatitis is two-fold. On one hand, it can be used diagnostically to determine the nature of collections, to establish the presence of infection, to recognize the actual pathogen, and to help direct specific antimicrobial therapy. On the other hand, the infected collections can be drained through a percutaneous catheter, thus obviating the need for an open operative procedure. Fluid collections in the vicinity of the pancreas that are found within a few weeks of the onset of acute pancreatitis should not be treated as if they were pseudocysts (9). Some recent reports advocate the use of imaging guided techniques for patients with a variety of complications of acute pancreatitis with promising results (52, 53, 54, 89, 90). Pseudocysts result most commonly from an attack of pancreatitis associated with disruption of the pancreatic duct. The treatment of pseudocysts has evolved over recent years from the operative drainage of all pseudocysts larger than 6 cm to a more selective approach, because serial imaging has documented that many pseudocysts resolve spontaneously. The presence of symptoms arising from compression by the pseudocyst of adjacent organs, causing abdominal pain, nausea, vomiting or jaundice, together with a six week interval period to allow maturing of the cyst wall, are the principal factors in deciding to drain a pseudocyst. Sterile pseudocysts can be drained internally by anastomosing the pseudocyst to the stomach, jejunum or duodenum. Endoscopic stenting of the pancreatic duct can be useful in selected patients, but the long-term outcome is unknown. Coupled with successful stenting of the duct, or in patients with normal pancreatic duct ana-
tomy, percutaneous drainage of associated pseudocysts has resulted in satisfactory clinical outcomes and resolution of the pseudocyst (9, 91). Furthermore, infected pseudocysts should be drained externally because the relatively small percutaneous drains usually do not adequately evacuate the debris and necrotic matter in the cyst.

**Necrosectomy**

The operative debridement of infected necrosis of the pancreas has been considered a mainstream tool in the management of the 2% to 5% of patients with severe acute pancreatitis associated with pancreatic necrosis (1, 2, 52). Although operative treatment of this condition continues to evolve, it is recommended in patients who continue to deteriorate despite optimal non-operative treatment, or who develop infected necrosis (9, 92, 93). The operative goal is removal of all necrotic pancreatic and peri-pancreatic tissue that serves as a nidus for infection and sepsis. Operative techniques for managing persistent or recurrent necrosis after initial necrosectomy include serial abdominal explorations with wide drainage, high volume lavage, and open or closed packing. Studies have been conducted to establish the optimal time to perform the necrosectomy, showing an overall worse outcome in patients who undergo early debridement compared with patients who undergo late debridement (52, 94). Different surgical approaches are utilized, and no evidence exists to demonstrate the superiority of one over the others (1, 2, 52, 53, 94). Because percutaneous catheter drainage or aspiration has little or no value in evacuating the thick necrotic material and can actually increase the risk of resistant infections, this approach cannot be recommended. New minimally invasive procedures are currently being used in some institutions, but the lack of a comparative trial of significant size to date, limits positive recommendations for their use until additional experience and data have been accumulated and analyzed. However, in patients who are at high risk for open operative treatment, endoscopic transgastric drainage of pancreatic necrosis and pseudocysts is a promising new alternative management (9, 95, 96). Finally, it should be understood that peritoneal lavage and pancreatic resection have no proven value in treating necrotizing pancreatitis (9).

**Treatments of limited or unproven value (2)**

Although peritoneal dialysis was intended to eliminate the proinflammatory factors released into the abdomen during severe acute pancreatitis and possibly reduce the severity of the systemic response, a recent prospective, randomized, multi-institutional study showed it to be of no benefit. Though useful in providing patient comfort during the early stages of the attack when nausea and vomiting are common occurrences, subsequent nasogastric decompression does not appear to alter the course or outcome of acute pancreatitis. Other mechanisms for reduction of gastrointestinal and/or pancreatic secretion, including H2 receptor blockers, proton pump inhibitors, antacids, atropine, somatostatin, glucagon, and calcitonin, have not shown beneficial effects on the outcome of acute pancreatitis. Similarly, anti-inflammatory agents including steroids, prostaglandins, and indomethacin have not been helpful in treating pancreatitis. Inhibition of activated proteolytic enzymes by aprotinin or gabexate mesylate fail to alter the course of pancreatitis unless their use is begun prior to the onset of the acute attack. Obviously, this has limited practical value clinically other than as prophylaxis against ERCP induced pancreatitis. Other approaches which have also been evaluated in experimental models of pancreatitis such as hypothermia, plasmapheresis, thoracic duct drainage, procainamide, isoproterenol, heparin, dextran and vasopressin have also shown little evidence of clinical usefulness. Finally, because platelet-activating factor (PAF), a proinflammatory agent, has been shown to aggravate experimental pancreatitis in animals, several recent clinical trials have been designed to apply this knowledge to patient management, but have failed to show that anti-PAF agents have any value in altering the outcome of patients with severe pancreatitis.

**Summary (9) and Recommendations (94)**

The spectrum of clinical presentations of acute pancreatitis depends on the severity of the disease process and varies from a mild transitory form (80%) which is self-limiting, and usually subsides spontaneously in 3 to 5 days, to a severe necrotizing disease (15% to 20%). The classic clinical presentation of acute pancreatitis consists of constant epigastric
pain of insidious onset, often radiating to the back, and accompanied by anorexia, fever, nausea, vomiting, ileus and abdominal distention and tenderness. Although no single laboratory test is pathognomonic for pancreatitis, several scoring systems have been designed to assess the severity of acute pancreatitis, to assess the risk of complications and to categorize patients into groups at high risk for complications. (Ranson, Imrie, Glasgow, APACHE II). Contrast-enhanced dynamic CT has become the standard test for evaluating patients with acute pancreatitis and diagnosing pancreatic necrosis. Ultrasonography is useful in mild cases of acute pancreatitis to assess for gallstones. The primary goals in treating patients with acute pancreatitis are to provide supportive therapy and to minimize development of complications; to limit the severity of the pancreatic inflammatory process and the systemic inflammatory response; and to treat any specific complications that might occur. Supportive therapy should include adequate and prompt resuscitation with intravenous fluids, supplemental oxygen, analgesics, and nothing by mouth after initial nasogastric decompression of the stomach. In patients with more severe disease or co-morbidities, ventilator assistance to provide optimal oxygenation, inotropic drugs, and hemofiltration or dialysis may also be required. In most patients with mild pancreatitis, gastrointestinal tract rest with adequate fluid resuscitation is usually sufficient initial management. The oral route for feeding should be re-established as soon as the nausea subsides and provided that the pain does not reappear upon feeding. If ileus or pain persists beyond five days, or if the pancreatitis is severe, parenteral nutrition should be initiated for nutritional support. Additionally, the comprehensive treatment of acute pancreatitis should include the removal of the etiology of the initiating factor, such as biliary tract decompression or cessation of alcohol ingestion, as indicated.

Approximately 2% to 5% of patients develop severe pancreatitis that is associated with pancreatic necrosis. The rationale for operative treatment is removal of the necrotic peri-pancreatic and pancreatic tissue that acts as a reservoir for infection and sepsis. Acute peri-pancreatic fluid collections found within a few weeks after the onset of pancreatitis tend to resolve spontaneously and should not be mistaken for, or treated as if they were, pseudocysts.

Considerable progress in the understanding of the pathogenesis and treatment of acute pancreatitis is based on the recent finding that the initiation of the disease occurs within the acinar cells. Additional knowledge of pancreatic physiology and pathophysiology will undoubtedly accrue further from studies of the well characterized properties of human enzymes that are involved in the initial activation cascade, and will likely advance the development of more effective strategies for the prevention and treatment of this challenging disease in the future (30).

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Adress correspondence: 56 Franklin Street, Waterbury, Connecticut 06706, USA