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# **ACUTE AND CHRONIC PANCREATITIS**

**New concepts and  
evidence-based approaches**



**EDIZIONI MINERVA MEDICA**

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# PREFACE

Great advances have been achieved in recent years in our understanding of the inflammatory diseases of the pancreas and in their clinical management.

In this book, the Editors tried to highlight areas of particular interest regarding acute, chronic and recurrent pancreatitis, both reporting new concepts and evidence-based approaches. This book has not been designed to cover all areas of pancreatic disease in exhaustive detail, but rather to stimulate the reader with up-to-date reviews in areas where major progress has been made, including therapeutic pancreatic endoscopy and ultrasound endoscopy.

Contributors of different countries, from Europe to USA, were also asked to provide evidence-based approaches that can guide diagnostic and therapeutic algorithms in the clinical practice.

Advances in diagnostic techniques, including imaging modalities, have improved the diagnostic yield of the inflammatory diseases of the pancreas and, in particular, differentiation among benign and malignant pancreatic lesions. In the same way, technical advances have increased the effectiveness of the endoscopic treatment of pancreatitis, nowadays extended to the management of local complications which were before prerogative of the surgery alone.

Compared to acute and chronic pancreatitis, recurrent pancreatitis remains the inflammatory disease of the pancreas that still raises more difficult issues, regarding the pathophysiology and the evolution of the disease, as well as the diagnostic and therapeutic work-up.

This book must go to our readers, not only gastroenterologists and endoscopists, but also expert in internal medicine and surgery. All those with an interest in inflammatory pancreatic disease should find something worthwhile. We hope there will be many who will find a stimulus from these pages.

Topics in medical gastroenterology, endoscopy, radiology and surgery have been addressed in the hope that our readers will include not only established specialists but also practicing clinicians, fellows, and students as well.

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# PATHOPHYSIOLOGY OF ACUTE DAMAGE

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Acute pancreatitis is an entity characterized pathologically by edema, inflammation and various degrees of parenchymal cell injury and death such as disorganization of cellular ultrastructure, necrosis and apoptosis.

Clinically, Atlanta classification differentiates a mild form, corresponding to a pathological feature of interstitial oedema and clinically associated with minimal organ dysfunction and a rapid recovery, and a severe form, associated with development of pancreatic necrosis with the onset of organ failure and/or local (such as necrosis, infection, pseudocyst and/or abscess) and systemic complications (failure of various organs), with a significantly higher risk for surgery, death and a slower recovery, conditioning a longer hospital stay.

In the last two decades of the last century, considerable progress has been made in advancing our understanding of the early cell biological events and the mechanisms that underlie the onset and progression of acute pancreatitis.

The main pathophysiological key points are:

- the mechanisms that determine the onset of acute pancreatitis;
- the sterile inflammatory systemic response;
- the infection stage.

## THE FIRST STEP: TRIGGER OF THE INFLAMMATION

### *Early intra-acinar events*<sup>1</sup>

Acute pancreatitis is the result of the autodigestion of the pancreatic gland. It can be triggered from various events or agents that are still not completely identified. However, independently from the cause, the main initial event seems to arise in the pancreatic acini.

Under physiological conditions, potentially harmful digestive enzymes are synthesized and secreted by acinar cells as inactive proenzymes or zymogens. After stimulation by neurohormonal secretagogue, in particular cholecystokinin (CCK), acinar cells release zymogen granules into the pancreatic ductal system where they are discharged in inactive state into the duodenal lumen. Pancreatic digestive enzymes are then activated in duodenum when exposed to a low pH and are processed by the intestinal enterokinase, a proteolytic enzyme placed in the brush-border of enterocytes. Enterokinase cleaves the NH<sub>2</sub>-terminal trypsinogen-activation peptide (TAP) from trypsinogen, releasing active trypsin that activates all the other zymogens.

In the early stages of pancreatitis, trypsinogen is prematurely and inappropriately activated in the pancreas rather than into the intestinal lumen.<sup>2</sup>

Experimental models showed that in the first steps of acute pancreatitis the transport of zymogens and in particular the discharge of pancreatic enzymes in the acinar lumen (*exocytosis*) is altered. The digestive enzyme synthesis and intracellular transport continue during the early stages of pancreatitis, but secretion of newly synthesized digestive enzymes from acinar cells is blocked. The consequence of this block is the formation of *condensing vacuoles*, derived from fusion between newly synthesized zymogens and the lysosome containing hydrolases. This catabolic process is called *crynophagy* and it is present in all human cells to degrade not used cytoplasmic cellular constituents and to recycle energy.

The contact between lysosomal hydrolases (probably cathepsin B) and pancreatic enzymes in an intra-vacuolar acid pH favors the intracellular activation of trypsin and, then, of all other pan-

creatic pro-enzymes.<sup>2</sup> The fragility of condensing vacuoles may facilitate the inappropriate intracellular release of activated enzymes,<sup>2</sup> causing cellular damage. However, it has been suggested that in experimental acute pancreatitis the auto-digestion doesn't take place only intracellularly, but it is also secondary to interstitial release and activation of trypsinogen. Indeed, the blockade of exocytosis may determine a basolateral migration of condensing vacuoles, their fusion with basolateral cellular membranes and the release of pancreatic enzymes and lysosomal hydrolases in the interstitial space, causing cellular and vascular damage.<sup>3</sup>

Calcium ( $\text{Ca}^{2+}$ ) may also play an important role in early acute pancreatitis. Despite hypocalcemia is a frequent finding in patients with severe acute pancreatitis, it is mainly secondary to the loss of  $\text{Ca}^{2+}$  bound to albumin in the third space, with an higher concentration of extra-cellular  $\text{Ca}^{2+}$ . Extracellular calcium increases cytosolic calcium dose-dependently.<sup>4</sup> Increased levels of intra-acinar calcium elicit a disruption of acinar cell ultrastructure, secretory blockade, premature activation of trypsinogen and blockade of trypsin inactivation, ATP depletion. Experimentally, hyperstimulation by supramaximal doses of secretagogues, duct ligation, pH, relevant concentrations of bile acids and no oxidative alcohol metabolites lead to a sustained increases in cytosolic calcium.

Two trypsinogen cleavage sites are available for potential attack by trypsin, the arginine 122 (R122), which leads to trypsin inactivation, and the lysine 23, which cleavage activates trypsin with the release of the eight amino-acid trypsinogen activation peptide. The susceptibility of each of the two sites is regulated by the ambient concentration of calcium and concentration-dependent occupation of the calcium binding sites.<sup>5</sup>

Moreover, higher levels of  $\text{Ca}^{2+}$  can also activate nuclear factor  $\kappa\text{B}$  (NF- $\kappa\text{B}$ ), a transcription factor which is involved in the control of numerous immune and inflammatory response genes, such as activation of tumor necrosis factor alpha (TNF- $\alpha$ ) transcription.

This effect of pathologic calcium signaling is in accordance with the progression of local and systemic inflammation in acute pancreatitis not requiring trypsinogen activation. NF- $\kappa\text{B}$  is activated early in acinar cells, independently of trypsinogen activation, and might be responsible for progression of the disease.<sup>6</sup>

Pancreatic ductal cells are probably a not silent bystander but may play an important role in the early events of acute pancreatitis. The reduction of bicarbonate and water secretion and/or alteration of the physiologic pH have been involving in the pathogenesis of acute pancreatitis. The secretion of bicarbonate is promoted by  $\text{Cl}^-$  released mainly from the acinar cells and ductal cells proximal to the acinar cells. The  $\text{Cl}^-$  is exchanged for bicarbonate by the luminal anion exchanger, resulting in bicarbonate secretion. Thus, damage to the  $\text{Cl}^-$  transport of acinar cells will decrease bicarbonate secretion from ductal cells.<sup>7</sup> A normal ductal fluid secretion is an important defense mechanism, since it may flush out toxic substances from pancreatic ductal lumen. The reduced secretion of bicarbonates and water may alter this defense mechanism, increasing the concentration of pancreatic enzymes and, therefore, the risk for activation of trypsinogen and reducing the intraductal pH.

The effect of oxidative stress in acute pancreatitis is so far not clear. Recent investigations reported that reactive oxygen species induction in the acinar cells promoted apoptosis while their inhibition led to an increased necrosis accompanied by reduced ATP.<sup>8</sup> These findings are quite surprising since it is well known that the oxidative stress is responsible for the propagation of the local and the systemic inflammation.

From these brief overview, the early events of pathophysiology of acute pancreatitis are complex, involve different component (acini, ductal cells, interstitial space) and are probably the results of several phenomena not yet completely understood.

## ***Triggering mechanisms***

### **Biliary pancreatitis <sup>7</sup>**

Different mechanisms have been proposed to explain the strong association between biliary lithiasis and acute pancreatitis. The most probable first event of biliary pancreatitis is an obstruction of the pancreatic ductal system secondary to a stone impacted in the papilla or consequent to papillary edema after calculus migration. Reflux of bile acids into the pancreatic ductal system has been postulated to explain gallstone pancreatitis. In experimental models, low concentration of bile acids in the main pancreatic duct stimulates the ductal secretion favoring its clearance and protecting

against pancreatitis. High concentrations, on the contrary, inhibit the ductal secretion inducing the early events of acute pancreatitis through a direct toxic effect or by increasing the cytosolic  $\text{Ca}^{2+}$ . This latter findings support the theory that ductal cells act as guards of acinar cells. Moreover, if the bile is infected with bacteria, the toxicity is increased also because non conjugated bile salts converted from bacterial hydrolase can pass through the cell membrane by passive diffusion, while conjugated bile acids are impermeable to cell membranes.

### Alcoholic pancreatitis <sup>9</sup>

Alcohol has been reported as strongly associated with acute pancreatitis in the past. However, more recent studies reported a low frequency of alcohol abuse among patients suffering from acute pancreatitis. Many different potential mechanisms of alcohol damage on the pancreas have been postulated.

Alcohol may alter the balance between proteases activation and inhibition, contributes to oxidative stress, alters the lipids metabolism and damages cellular membranes. Ethanol can be metabolized via oxidative and non-oxidative pathways. It is suggested that the harmful pathway of ethanol metabolism are the non-oxidative, producing ethanol fatty acid ethyl esters (FAEE), that can induce sustained toxic calcium signal into the pancreatic acinar cell, damaging mitochondria, decreasing ATP levels and leading to necrosis. FAEE may also induce alterations of cellular membranes at any levels (cells, mitochondria, zymogen, and lysosomes), destabilizing cells and intracellular organelles and favouring the early events of acute pancreatitis.

Similarly to bile acids, pancreatic ductal fluid and bicarbonate secretion is stimulated by low concentration and inhibited by high concentrations of ethanol. There is probably threshold of this defense system that when overtaken leads to pancreatitis.

Alcohol can also stimulate NF- $\kappa$ B, which regulates cytokine expression and, therefore influencing the progression of the disease.

The effect of alcohol on the Oddi's sphincter is yet unclear. Anyway, endoscopic manometry studies on humans have showed that acute local alcohol instillation significantly increased the tone of the papillary sphincter.<sup>10</sup> Chronic alcohol intake may cause papillary and pancreatic exocrine dysfunction, which could play a role in increasing pancreatic duct pressure and thus inducing acute pancreatitis.<sup>11</sup>

### Hypertriglyceridemia <sup>12</sup>

Patients with type I hyper-lipoproteinemia for lipoprotein lipase (LPL) mutations or apolipoprotein C-II deficiency have an increased risk to develop acute pancreatitis. Since only a small proportion of patients with hypertriglyceridemia develop pancreatitis, it is probable that this alteration may be only a risk factor. In LPL deficient mice, a greater degrees of inflammatory response, hemorrhage and necrosis have been observed compared to wild-type mice.<sup>5</sup>

A rapid accumulation of the largest triglyceride containing lipoproteins (chylomicrons) leads to ischemic events in the pancreatic microcirculation. In addition, non esterified free fatty acids may lead to the release of inflammatory mediators and free radicals further contributing to pancreatic damage.<sup>9</sup>

### Hypercalcemia <sup>4</sup>

One mechanism that has been proposed for calcium-induced pancreatitis is that high serum calcium influences the intra-cellular calcium levels and thus the intracellular pathways. As reported above, calcium dependent activation of zymogen and trypsinogen may be the mechanism of this type of pancreatitis, which occurs in diseases like hyperparathyroidism and neoplasia associated hypercalcemia.

### Obstructive pancreatitis <sup>13</sup>

Every obstruction at any level of the pancreatic ductal system may induce acute pancreatitis. Therefore, strictures secondary to previous acute necrotizing pancreatitis as well as neoplasia of the pancreas, of the papilla of Vater or of the common bile duct, benign or malignant, can induce acute pancreatitis.

Also intraductal papillary mucinous neoplasia (IPMN) might cause acute pancreatitis due to the obstructive effect by the tumor itself or by mucus.

### Gene mutations <sup>14</sup>

PRSS1, SPINK1, CFTR and CTSC gene mutations have been found associated with pancreatitis.

The mutations on cationic trypsinogen gene (PRSS1), the most abundant isoform of trypsinogen in human pancreatic juice,<sup>15</sup> enhance trypsinogen autoactivation and inhibition of the autolysis of the enzyme, leading to acute episodes of pancreati-

tis due to the inappropriate activation of pancreatic enzymes within the acini. Mutation in the anionic trypsinogen gens have been shown to be protective against pancreatitis, while no mutations of mesotrypsinogen of significance in human disease have been described to date.

The mutations on CFTR gene may be a cause of pancreatitis secondary to duct obstruction caused by insufficient electrolyte and fluid secretion by pancreatic ductal cells, altered pH and protein plugs formation. They may also determine pancreatitis by a primary defect in membrane trafficking at the apical plasma membrane acinar cells inducing a diminished pancreatic acinar secretion.<sup>16</sup> However, since heterozygosis carriers are 3-4% of general population in Western countries, these mutations may only increase the risk for developing pancreatitis.

The mutations on SPINK1 gene encoding for PSTI, a specific trypsin inhibitor markedly up regulated in the context of active inflammation, may induce acute pancreatitis reducing antiproteases activity.<sup>17</sup>

Finally, the mutations in chymotrypsin C, an enzyme that cleaves and destroys prematurely activated trypsin,<sup>18</sup> reduces the second line defense activity against trypsin activation.

## THE SECOND STEP: THE SYSTEMIC INFLAMMATORY RESPONSE <sup>19</sup>

After the initial local pancreatic inflammation, trypsinogen and activated digestive enzymes may be drained in the nodes or in the blood, or, if activated, may be blocked by PSTI and/or  $\alpha$ 1-antitrypsin or destroyed by proteases, such as trypsin, mesotrypsin or enzyme Y. If the activation is limited and the defensive mechanism works correctly, a mild, edematous acute pancreatitis is observed. On the other hand, if the activation is massive, the trypsin inhibitors with other protective factors are qualitatively altered or quantitatively diminished, severe autodigestive damages may start and the pancreatitis quickly becomes necrotic. The extent of the inflammatory phase of an episode of acute pancreatitis is thus dependent on the level of acinar cell damage. Resident macrophages and acinar cells are activated by the necrosis and release cytokines (mainly TNF $\alpha$ , IL6, PAF, IL1, IL8), that stimulate the recruitment and the activation of other leucocytes, particularly mono-

cytes and neutrophils, with a further release of cytokines and further activation of trypsinogen. These biologically active substances may enroll other inflammatory cells and, therefore, amplify a cascade the inflammatory process. Consequently, cytokines may recruit and activate inflammatory cells in remote organs (liver, spleen, kidney, and lung). Trypsin and other proteases may activate the systemic complement early in the course of acute pancreatitis, resulting in a central production of chemotactic mediators causes priming of circulating neutrophils and subsequent lung sequestration. The lung damage may be mediated by histamine, thromboxane or free radical, phospholipase A2, which can degrade the pulmonary surfactant, produced by neutrophils. These substances are biologically active and able to induce the severe pulmonary changes secondary to acute pancreatitis, similar to that observed during acute respiratory distress syndrome (ARDS)

The pathogenesis of systemic complications of acute pancreatitis is related to cytokines and kinins that are responsible of the evolution from a local inflammatory phenomenon to a systemic inflammatory response syndrome (SIRS). SIRS influence the onset of failure of vital organs (heart, liver, spleen, kidney, brain) and, later, a multi-organ dysfunction (MODs) and failure (MOF), similar to that observed in sepsis.

Neutrophil activation is an important determinant of severity of acute pancreatitis. Indeed, monocytes and neutrophil cells synthesize and release many other substances, like elastase, which can degrade vascular structures causing microcirculation disorders, interferon  $\alpha$  and  $\gamma$ , and oxygen free radicals. In particular, oxygen free radicals, physiologically produced as bactericidal and anti-neoplastic substances, are released in large quantities during acute pancreatitis and its high tissutal levels may determine severe lesions, both locally and systemically. The sudden and massive release of inflammatory mediators from polymorph-nuclear cells (PMN) may prolong their life by diminishing apoptosis (programmed death) and, therefore, favor an extended release of many mediators.

Furthermore, it has been demonstrated that TNF $\alpha$ , released from PMN and monocytes, may stimulate endothelial cells to product substances favoring micro-thrombosis (e.g. plasminogen activator inhibitor type-1), and expressing protein on cellular surface (e.g. intercellular adhesion molecule-1

– ICAM-1 – and E-selectin). The increased expression of these molecules on endothelial cell causes an increased of leukocyte-endothelial adhesion and trans-endothelial migration, with an increased cytokine-mediated tissue damage.

The pathogenesis of local and systemic complications of experimental acute pancreatitis may help to understand what happens in human disease. Necrosis of the pancreatic tissue represents the key step that influences the outcome of acute pancreatitis. In the absence of necrosis (edematous pancreatitis) the acute pancreatitis is clinically mild, with absence of complications and mortality. In the presence of necrosis, the disease may become clinically severe, with the onset of complications and mortality (up to 20%). The extension of necrosis has been demonstrated directly correlate with the severity of the acute pancreatitis.

A modern pathogenetic opinion postulated that pancreatic enzymes and the amplitude of cytokines activation contribute to the onset of SIRS, MODs and MOF. In other words, the local inflammatory process may extent to distal organs by the release of both proteases and cytokines from pancreas.

Consequently, the therapeutic rationale to prevent and treat acute pancreatitis, by reducing the severity of the disease, should be addressed to the two main causes that influence the evolution of the disease:

- to limit the autodigestive process mediated by proteases in the pancreas and, therefore, to prevent the extension of necrosis
- to block the diffusion of the disease to remote organs by reducing the systemic effects of cytokines.

### **THE THIRD STEP: THE SYSTEMIC INFECTIOUS RESPONSE <sup>20</sup>**

The outcome of the patients affected with severe acute pancreatitis is dependent upon two main complications of the local disease: the first “hit” is the toxic inflammatory (sterile) phase which occurs within 1-2 weeks after the onset of the clinical symptoms and is characterized by the release of pancreatic enzyme and cytokines in the systemic circulation. That triggers SIRS which leads to single or MOF, called “sterile MOF”, with cardio circulatory, pulmonary, renal and neurological impairment, as described above. The second “hit” is the infection MOF, occurs within 3-4 weeks

and is characterized by the super-infection of the necrotic pancreatic and peri-pancreatic collections. From 40% to 70% of patients with severe acute pancreatitis develop a secondary infection of the pancreatic necrosis and the mortality in these cases rises up to 40%.

The infection is due to bacterial translocation from the gut to the injured pancreas. In acute pancreatitis, the inflammatory response may impair the intestinal barrier allowing bacterial to enter in the circulation and after in the pancreatic necrotic tissue. The fluid loss in the retroperitoneum and in the third space may lead to hypovolemia and circulatory shock. The physiological response to shock is to shift the blood flow to the central organs (brain, lung, heart) impairing the splanchnic circulation. That leads to intestinal vasoconstriction, ischemia, mucosal acidosis, ATP depletion, increase of permeability because of changes in the tight junction and apoptosis of the epithelial cells, damage of the mucosal barrier and villi as a consequence of arteriovenous shunting.<sup>21</sup> Moreover cytokines like TNF contribute to increase the inflammation and thus the permeability of the mucosal cells.

- The mechanism of translocation can be multiple:
- bacteriemia;
  - transmural migration through the colonic bowel wall directly to the pancreas;
  - via ascites;
  - via the lymphatic to the circulation;
  - biliary duct system;
  - from the duodenum to the main pancreatic duct.<sup>22</sup>

The exact mechanism is yet still not known and difficult to demonstrate. However, recent investigations showed in experimental models on rats that bacterial translocation occurs mainly via mesenteric lymph node draining bacteria from the small bowel.<sup>23</sup> According to this work, colonic decontamination did not decrease the pancreatic superinfection rate, while with selective decontamination of the small bowel the infection rate was reduced significantly. These results showed that bacterial overgrowth in the small bowel, also enhanced from reduced bowel motility particularly in the cases of acute pancreatitis with intestinal paralytic ileus, might be a crucial event in the pathophysiology of this complication. Trans-peritoneal pathway of bacterial spreading seems to be unlikely, since

peritoneal cavity physiologically prevents bacterial diffusion.<sup>22</sup>

The bacteria usually isolated from pancreatic necrotic tissue are aerobic gram negative, like *E. Coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter*, *Proteus*, that are the constituent of the gastrointestinal flora. In the majority of the cases (60-87%) a single germ may be isolated, whereas in the remaining cases more than one bacterium is present. Although most of the pancreatic infections are due to gram-negative species, also gram-positive bacteria can be found. Mortality is high with gram-negative species, while gram-positive germs are associated with a significantly lower mortality. The incidence of fungi may increase after prolonged antibiotic treatment, and mortality increase up to 60% of cases. This may be related to the fungi, but more probably to the immunosuppression predisposing to the fungal infection. Candidiasis is reported in up to 20% of patients with infected pancreatic necrosis.

According to these evidences enteral feeding is probably the best nutritional support for patients with acute pancreatitis, since improve the intestinal permeability, preventing the intestinal atrophy secondary to fasting, and reduce the overgrowth of microflora by restoring the physiological motility.

Also selective gut decontamination with not absorbable antibiotics seems to be a correct approach to the disease.

## CONCLUSIONS

Pathophysiology of acute pancreatitis is complex and extremely variable, but it seems to follows some steps that correlate with specific clinical events. The therapeutic approach should follow these steps to try to prevent the complications of the disease, to reduce the need for surgery and to improve the outcome of patients. Despite no specific treatment of acute pancreatitis is still available, the full understand of the mechanism of acute pancreatitis may suggest the practical use of drugs able theoretically to modify the natural history of acute pancreatitis. However, the evidence-based efficacy of these drugs will be proven only taking into account the extreme variability of the clinical picture of the disease. In other words, only clinical trials including carefully selected patients for a specific aim will demonstrate the efficacy of a single drug.

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# ACUTE PANCREATITIS: AETIOLOGY

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There are numerous aetiological factors of acute pancreatitis. However, the most frequent causes of acute pancreatitis are biliary obstruction and alcohol consumption which are accounting for about 75 percent of cases (Table 2-I).

In 10-20% of the patients aetiology remains unclear. The number of these cases diagnosed as "idiopathic" however are decreasing as our understanding of acute pancreatitis improves. Other causes of acute pancreatitis are generally seldom and differ considerably in between studies.

This may largely be due to geographical differences in patient population and experience of the treating physicians.

## GENETIC CAUSES

Genetic mutations have long been suspected to be associated with hereditary pancreatitis. These forms of inherited pancreatitis may present as recurrent episodes of acute pancreatitis but will eventually progress to chronic pancreatitis.

### PRSS1

A clear autosomal dominant inheritance pattern was observed in some families with hereditary pancreatitis, suggesting a single molecular defect. Further research using genetic linkage stud-

ies was able to pinpoint the locus to chromosome 7 and in 1996 Whitcomb and colleagues finally identified the responsible gene.<sup>1</sup> The mutation was identified in the third exon of the serine protease 1 gene (PRSS1) on chromosome 7q35, which encodes cationic trypsinogen. This first identified mutation results in an arginine to histidine substitution (p. R122H "classic" mutation) leading to loss of function at the autolysis site of trypsin. To date, more than 20 mutations have been associated with hereditary pancreatitis and new mutations continue to be described. By far the most common pancreatitis-associated mutations in PRSS1 are the p. R122H and the p. N29I mutations, which were shown to be present in 78% and 12%, respectively, in a large French series of 200 patients from 78 families with hereditary pancreatitis.<sup>2</sup> The authors estimated the prevalence of hereditary pancreatitis in this study to be at least 0.3 per 100,000. Furthermore, a high penetrance of these p. R122H and p. N29I mutations of 80 to 90 percent was reported. Why some family members with these mutations do not develop pancreatitis remains unclear. It has been suggested that the presence of additional mutations that protect against the development of pancreatitis could be a possible explanation and one such mutation in the PRSS2 gene, resulting in the loss of trypsin activity, has recently been described.

**Table 2-I** Largest recently published studies on aetiology of acute pancreatitis.

Authors	Date	Patients (n)	Men (%)	Women (%)	Aetiology biliary	Alcohol	Ideopathic
Vinklerová <i>et al.</i>	2010	170	53	47	53	31	
Roberts <i>et al.</i>	2008	55215	52	48	27,2	6,5	
Appelros <i>et al.</i>	1999	547	58	42	38,4	31,8	23,2

## CFTR

Other mutations that can cause acute pancreatitis have been identified in the cystic fibrosis transmembrane conductance regulator gene (CFTR) and present in an autosomal recessive pattern. Some but not all of these mutations that cause acute pancreatitis are associated with manifestations of cystic fibrosis because the severity of disease manifestations depend on the severity of the mutation and zygosity.<sup>3</sup> Patients with non-functional CFTR Protein show typical clinical signs for cystic fibrosis including exocrine pancreatic insufficiency and recurrent acute and consequently chronic pancreatitis. Patients with less severe mutations (e.g. CFTR R75Q mutations causing a selective defect in bicarbonate secretion but not chloride secretion as in classic cystic fibrosis) in the CFTR gene may show a less-functional CFTR Protein with limited features of cystic fibrosis. These patients still have a considerable risk to develop pancreatitis, which has been estimated to be 40 to 80-fold increased over the general population.<sup>4</sup> Patients that are heterozygotes for CFTR mutations are generally healthy but still have a 3 to 4-fold increased risk over the general population to develop pancreatitis. However, several studies have suggested that additional genetic or environmental disease modifiers are probably necessary in these CFTR mutation carriers to actually develop pancreatitis.

## SPINK1

Another group of mutations that predispose to pancreatitis are mutations in the serine protease inhibitor **K**azal type **1** gene (SPINK1). SPINK1 has a protective action in the pancreas since it serves as a critical feedback inhibitor of trypsin. Therefore, in a state of retained SPINK1 protein function due to a (mostly heterozygous) SPINK1 gene mutation, the pancreas is more susceptible to develop pancreatitis from other genetic or environmental factors.

It has been repeatedly shown that 16-23% of patients with apparent idiopathic pancreatitis show SPINK1 mutations while only about 2% of healthy controls showed similar mutations.<sup>5</sup> Finally, SPINK1 mutations have been estimated to increase the risk for pancreatitis about 12-fold over the general population.

## OBSTRUCTIVE (BILIARY/PANCREATIC) CAUSES

### Gallstones

Gallstones are the most common cause of acute pancreatitis, which accounts for 35-40% of all cases.<sup>6</sup> The peak incidence for biliary pancreatitis is between 50-60 years of age and obesity is a frequent feature in these patients. The risk to develop acute pancreatitis in patients with gallstones is greater in male patients while the overall incidence of gallstone pancreatitis is greater in female patients since they are more frequently affected by gallstone disease as such.<sup>7</sup> The exact pathomechanism by which the passage of gallstones induces pancreatitis is still unknown. It is believed that gallstones may cause a (temporary) obstruction at the ampulla, leading to reflux of bile flow into the pancreatic duct and consequent acute pancreatitis.<sup>8</sup> However, in the majority of patients with biliary pancreatitis, gallstones are found in the gallbladder but not in the common bile duct and only 3-5% of patients with acute pancreatitis have been reported to have stones impacted at the ampulla.<sup>9</sup> Nevertheless, the cause-effect relation between gallstones and acute pancreatitis becomes evident when looking at the fact that cholecystectomy and/or cleaning the common bile duct prevents recurrence. The incidence and frequency of pancreatitis is closely related to the size of the stones, where small stones (diameter <5 mm) have a significantly higher risk to pass through the cystic duct and cause acute pancreatitis.<sup>10</sup> Patients with biliary sludge (a viscous bile suspension that may contain small stones <5 mm) and/or gallbladder microlithiasis are therefore especially prone to develop acute biliary pancreatitis.

### Tumours

Both pancreatic and periampullary cancer may induce acute pancreatitis. The incidence of pancreatitis in these patients has been reported to be around 14%. As for gallstone pancreatitis, a partial or complete pancreatic outflow obstruction and/or bile reflux have been suggested as potential pathomechanisms. The severity of pancreatitis in these patients was reported to be rather mild. Intraductal papillary mucinous neoplasms (IPMNs) are increasingly recognised cystic pan-

creatic tumours arising from the pancreatic ducts and may occasionally present as acute pancreatitis, especially in elderly males without a history of alcohol. The reported rate of acute pancreatitis in these patients varies widely between 12-67% and as in patients with pancreatic or periampullary cancer, the severity was reported to be rather mild.<sup>11</sup>

### ***Pancreas divisum***

Pancreas divisum results from incomplete fusion of the embryologically derived dorsal and ventral pancreas, resulting in two separate pancreatic ductal systems. It is a fairly common anatomic variant, occurring in about 7% of autopsy series. The accessory papilla and duct have been hypothesized to be too small to ensure pancreatic outflow, leading to obstructive pain and pancreatitis. However, whether pancreas divisum is related to acute pancreatitis or is an incidental finding is still controversial.

### ***Other obstructive causes***

Other rare conditions that have been associated with acute obstructive pancreatitis include ampullary stenosis, periampullary duodenal diverticulae, duodenal stricture or obstruction, and helminthic obstruction by ascariasis.

## **METABOLIC CAUSES AND DRUGS**

### ***Alcohol***

Excess alcohol consumption is the predominant etiology in men, responsible for about 30% of all cases of acute pancreatitis in the United States.<sup>12</sup> Patients with alcohol induced acute pancreatitis typically report of consumption of large amounts of alcohol for at least 5-10 years prior to the first attack. If acute attacks are recurrent, most patients are thought to develop subsequent chronic pancreatitis. This long thought causality has been increasingly questioned recently and it has been suggested that acute alcoholic pancreatitis may only develop with preexisting chronic pancreatitis and not vice versa.<sup>13</sup> The underlying mechanisms, however, are incompletely understood. Alcohol intake causes a transient stimulation of exocrine pancreatic secretion by increasing the synthesis and secretion of digestive and lysosomal enzymes in pancreatic aci-

nar cells.<sup>14</sup> Furthermore, alcohol has been shown to sensitize pancreatic acinar cells to cholecystokinin and may have a direct toxic effect on the acinar cells. However, these mechanisms alone are probably not sufficient to cause acute pancreatitis. Therefore, additional genetic and environmental factors are thought to influence the development of the disease.

### ***Smoking***

Smoking has long been thought to play a role in the induction of acute pancreatitis, but it was only recently that large prospective studies could prove cigarette smoking to be an independent risk factor for acute pancreatitis. In the most recent study, Sadr-Azodi *et al.* were able to show that the risk of non-gallstone-related acute pancreatitis was more than double among current smokers with  $\geq 20$  pack-years of smoking as compared with never-smokers.<sup>15</sup> Furthermore, it became evident that the duration of smoking rather than smoking intensity increased the risk of non-gallstone-related acute pancreatitis. Only after two decades of smoking cessation the risk of non-gallstone-related acute pancreatitis was reduced to a level comparable to that of non-smokers.

### ***Drugs***

First reports in the 1950s suggested that certain medications like cortisone and chlorothiazide may induce acute pancreatitis. Since then, the number of suspected drugs has been ever increasing. At the time of writing, more than 100 substances have been identified that may induce acute pancreatitis (Table 2-II). However, discrepancies have been identified between studies including inconsistency in the time interval between drug application and onset of disease (latency). Therefore, Badalov *et al.* established a classification system for drugs that have been suspected to induce acute pancreatitis based on the number of cases reported, the existence of rechallenge trials, consistency in latency in between reported cases, and the exclusion of other causes.<sup>16</sup> They classified drugs with at least one case report with positive rechallenge and exclusion of other possible causes as *class Ia*, drugs with at least one case report with positive rechallenge without exclusion of other possible causes as *class Ib*, drugs that have been reported in more than 4

cases with consistent latency as *class II*, drugs with reports of at least 2 cases without consistent latency as *class III*, and single case reports as *class IV* (Table 2-II). According to their classification, drugs in class I and II are thought to have the greatest risk to induce acute pancreatitis. Multiple

mechanisms have been suggested by which drugs may induce pancreatitis. These are closely associated to the specific effect of the respective drug and include direct toxic effects, immunologic reactions, ischemia, and increased viscosity of pancreatic juice.

**Table 2-II** Drugs suspected to induce acute pancreatitis based on drug class.<sup>15</sup>

Ia	Ib	II	III	IV
$\alpha$ -methyl dopa	All-trans-retinoic acid	Acetaminophen	Aledronate	Adrenocorticotrophic hormone
Azodisalicylate	Amiodarone	Chlorthiazide	Atorvastatin	Ampicillin
Bezafibrate	Azathioprine	Clozapine	Carbamazepine	Bendroflumethiazide
Cannabis	Clomiphene	Didanosine	Captopril	Benzapril
Carbimazole	Dexamethasone	Erythromycin	Ceftriaxone	Betamethazone
Codeine	Ifosfamide	Estrogen	Chlorothalidone	Capecytabine
Cytosine	Lamivudine	L-asparaginase	Cimetidine	Cisplatin
Arabinoside	Losartan	Pegasparagase	Clarithromycin	Colchicine
Dapsone	Lynesterol/methoxyethinylestradiol	Propofol	Cyclosporin	Cyclophosphamide
Enalapril	6-mercaptopurine	Tamoxifen	Gold	Cyproheptidine
Furosemide	Meglumine		Hydrochlorothiazide	Danazol
Isoniazid	Methimazole		Indomethacin	Diazoxide
Mesalamine	Nelfinavir		Interferon/ribavirin	Diclofenac
Metronidazole	Norethindronate/mestranol		Irbesartan	Difenoxylate
Pentamidine	Omeprazole		Isotretinoin	Doxorubicin
Pravastatin	Premarin		Ketorolac	Ethacrinic acid
Procainamide	Sulfamethazole		Lisinopril	Famciclovir
Pyritonol	Trimethoprim-sulfamethazole		Metalozone	Finasteride
Simvastatin			Metformin	5-fluorouracil
Stibogluconate			Minocycline	Fluvastatin
Sulfamethoxazole			Mirtazapine	Gemfibrozil
Sulindac			Naproxen	Interleukin-2
Tetracycline			Paclitaxel	Ketoprofen
Valproic acid			Prednisone	Lovastatin
			Prednisolone	Mefanamic acid
				Nitrofurantoin
				Octreotide
				Oxyphenbutazone
				Penicillin
				Phenophthalein
				Propoxyphene
				Ramipril
				Ranitidine
				Rifampin
				Risperidone
				Ritonovir
				Roxithromycin
				Rosuvostatin
				Sertaline
				Strychnine
				Tacrolimus
				Vigabatin/lamotrigine
				Vincristine

## Hypercalcemia

Hypercalcemia was suggested to be able to induce acute pancreatitis by direct activation of trypsinogen in the pancreatic parenchyma and by deposition of calcium in the pancreatic duct. The most common cause of hypercalcemia is hyperparathyroidism. Multiple clinical reports have associated primary hyperparathyroidism with acute pancreatitis. However, the largest published series of 1153 patients with primary hyperparathyroidism showed that only 1.5% of patients developed acute pancreatitis, which was similar to the frequency in the general hospital population.<sup>17</sup> The causal connection between hyperparathyroidism and acute pancreatitis has therefore been increasingly questioned. It has recently been shown in an experimental model that only acute hypercalcemia, rather than chronic hypercalcemia, leads to ectopic trypsinogen activation and consequent acute pancreatitis in the rat.

## Hyperlipidemia

Patients with inherited forms of hyperlipoproteinemia types I and V suffer from severe hypertriglyceridemia and have been reported to develop attacks of acute pancreatitis. More recently, serum triglyceride concentrations above 1000 mg/dL (for both inherited and acquired forms of hypertriglyceridemia) have been shown to be associated with acute pancreatitis, while the true incidence is unknown and the underlying mechanisms are not understood.<sup>18</sup> On the other hand, elevated cholesterol levels have not been shown to be associated with pancreatitis.

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# DEFINING DISEASE SEVERITY: WHICH SCORE IS BEST?

F. Gallucci, G. Uomo

3

Over the last few decades, data from relevant series of patients suffering from acute pancreatitis (AP) have clearly shown that one of the most relevant features of the disease is the great variability in clinical severity and its outcome. Most patients (80-85%) present a mild and self-limiting disease whereas the remaining portion develops some major local and/or systemic complications, frequently leading to multiple organ failure and death. Physicians taking care of these patients should be aware that an accurate classification of the disease severity is crucial for its management. Selecting the patients with severe form of AP as early as possible after the onset of symptoms is basic for appropriate triaging/treatment, monitoring the disease's course, supporting clinical decision-making and rationalising health care resources. In addition, the identification of patients at risk for complications is valuable for accurate recruitment and stratification into clinical trials, mainly in studies designed for targeted intervention.

For a long time, the severity of AP has been classified as either 'mild' or 'severe' and have then been defined variably.<sup>1</sup> Over the last few years, the limitations of this dichotomy have become apparent since patients classified as "severe" disease comprise subgroups with very different outcomes. These subgroups include patients at higher risk of mortality due to persistent rather than transient organ failure, those without organ failure who are at higher risk of morbidity due to necrotizing rather than interstitial pancreatitis, and those with higher mortality when a combination of infected pancreatic necrosis and persistent organ failure is present.<sup>2</sup> Considering all factors influencing the clinical course and final outcome of the disease, an early valuable prognostic assessment is difficult in clinical

practice. Bedside clinical prognostic assessment, the usual *modus operandi* of good clinical practice, is inherently subjective, dependent on the assessor's expertise and experience. A number of early clinical findings (such as increasing age, fever, tachypnoea, Grey-Turner's and Cullen's signs, abdominal mass, prolonged paralytic ileus, obesity) have been reported as having prognostic value in AP but these findings are either not present in many patients with severe disease or take a long time to assess.<sup>3</sup> Furthermore, of these findings, only age, fever and body mass index can be objectively quantified. The few reports available on this subject have reported a correct identification of severe AP through clinical evaluation on admission in 40-64% of patients. These data confirm that the discriminating ability of clinical assessment *alone* is not satisfactory. Recent pancreatic literature is full of papers reporting a wide variety of single biochemical markers, scoring systems, and imaging procedures for predicting severe pancreatitis.<sup>4, 5</sup> A recent systematic review found 184 original studies that reported on 196 different predictors of severity in AP, with 78% of the studies reporting a statistically significant result for at least one predictor.<sup>6</sup> Therefore, we are faced with many presumably effective ways to predict the severity of AP, but most of these parameters have found no place in clinical practice, because of either low reliability, high complexity, expensiveness and inaccuracy when it comes to prediction of an individual patient's severity.<sup>7</sup> On the other hand, according to Ranson,<sup>8</sup> an ideal prognostic method should have several characteristics:

- objectivity;
- accuracy;
- simplicity;
- availability at diagnosis;

- non-invasiveness;
- quantitiveness;
- independence with regard to aetiology;
- independence with regard to patient's pre-existing disease;
- complication specificity;
- usefulness for disease course monitoring.

In addition, another characteristic of primary importance is that the prognostic indicators must be detected in the early phase of AP.

The aim of this chapter is to focus on the proposed prognostic parameters and scoring systems trying to identify those with high accuracy in clinical practice.

### PROGNOSTIC ASSESSMENT BY MEANS OF SINGLE LABORATORY MARKERS

In routine clinical practice, a single valuable prognostic marker is easier to use than scoring systems which are very often complex and difficult to apply. Single analytes reported to be of early prognostic value in AP are listed in Table 3-I. Most of these

markers have not yet confirmed their initial validity in further studies; in many instances, they have been correlated with the necrotic process rather than with clinical findings; in other cases, evaluation of effectiveness was based on small series of patients. Furthermore, the presence of concomitant diseases may influence serum levels of these factors, independent of the severity of AP. Of the more simple markers easily available in almost all hospitals, the most widely investigated and used is C-reactive protein (CRP). This serum marker showed a strong correlation with pancreatic and peripancreatic necrosis with a sensitivity and specificity greater than 80% and its serum level higher than 120-160 mg/L is more than likely associated with a severe course of AP.<sup>9</sup> However, CRP peaks about 72 hours from onset of symptoms, just at the end of the crucial time (*therapeutic window*) in AP, when most treatments should already be instituted. So, CRP is far from being optimal prognostic marker in the early phase of AP even if it may prove useful in clinical practice to monitor the course of the disease together with imaging examinations. Certainly, cytokines as markers of inflammatory response (in particular interleukin-6) are more accurate in the early phase to predict a severe course of AP, but limitations in their applicability in clinical practice are related to complexity and relative cost of lab determination.<sup>10</sup>

Recently, the prognostic powerful of the one of most simple laboratory parameter the blood urea nitrogen (BUN) was investigated on three prospective AP cohort studies.<sup>11</sup> The meta-analysis and stratified multivariate logistic regression adjusted for age, sex and creatinine levels were calculated to determine the risk of mortality associated with an elevated BUN level at admission and a rise in BUN level at 24 hours (1043 patients included in the pooled analysis). BUN level of 20 mg/dL or higher was associated with an odds ratio of 4.6 for mortality. Any rise in BUN level at 24 hours was associated with an odds ratio of 4.3 for mortality. The accuracy of the serial BUN measurement resulted comparable to that of the APACHE II (*acute physiology and chronic health examination*) score. Interestingly, another recent multicentre prospective study including 462 patients with AP showed that if serum creatinine is normal, necrotizing pancreatitis is unlikely to develop.<sup>12</sup> These results confirm the considerable relevance of the renal function as determinant of the AP outcome. BUN should be carefully considered as an early prognostic marker

**Table 3-I** Single analytes reported to be of early prognostic value in acute pancreatitis.

- Amylase
- Calcium
- White blood cells
- Blood glucose
- Haematocrit
- Phospholipase A2
- Coagulation factors
- Complement activation factors
- Polymorphonuclear (PMN) elastase
- Arterial hypoxemia
- Amyloid A
- Acidosis
- Methaemalbumin
- Ribonuclease
- Alpha1-protease inhibitor
- Alpha2-macroglobulin
- Endothoxin
- Trypsinogen activation peptide
- Pancreatitis-associated protein
- Tumor necrosis factor receptor antagonists
- Neopterin
- Interleukin 6
- Interleukin 8
- Phospholipase A2 activation peptide
- Procarboxypeptidase activation peptide (CAPAP)
- C-reactive protein
- Procalcitonin
- Creatinine
- Blood urea nitrogen

**Table 3-II** Multifactorial prognostic scores, year of initial report and associated parameter (bibliography of each score can be found in references <sup>1, 3, 5-7, 13, 15</sup>).

Ranson	1974	Admission: age, WBC, glucose, LDH, AST; 48h: Hct, Calcium, BUN, base deficit, fluid loss, pAO <sub>2</sub>
Glasgow	1984	pAO <sub>2</sub> , albumin, calcium, WBC, AST, LDH, glucose, BUN
Simplified prognostic criteria	1986	MAP, pAO <sub>2</sub> , urinary output, calcium, albumin
Hong Kong	1989	BUN, glucose
APACHE II	1989	Temperature, heart rate, MAP, respiratory rate, WBC, Hct, plasma sodium, plasma potassium, creatinine, arterial pH, venous bicarbonate, pAO <sub>2</sub> , alveolar/arterial pO <sub>2</sub> difference, age, GCS, CHS
Tran <i>et al.</i>	1992	MAP, heart rate, respiratory rate
Marshall	1995	MAP, FiO <sub>2</sub> /pAO <sub>2</sub> , GSC, platelet count, creatinine
SOFA	1996	MAP, FiO <sub>2</sub> /pAO <sub>2</sub> , GCS, platelet count, creatinine, urinary output, bilirubin
Talamini <i>et al.</i>	1996	Creatinine, chest x-ray abnormality
SIRS	2006	Temperature, heart rate, respiratory rate, WBC
POP	2007	Age, MAP, FiO <sub>2</sub> /PaO <sub>2</sub> , arterial pH, calcium, BUN
Panc-3	2007	Hct, BMI, pleural effusion
BISAP	2008	BUN, impaired mental status, SIRS, age, pleural effusion
Japanese severity score	2009	Base excess, pAO <sub>2</sub> , BUN, creatinine, LDH, platelet, calcium, CRP, SIRS, age
HAPS	2009	Abdominal tenderness, Hct, creatinine

WBC = white blood cells; BUN = blood urea nitrogen; MAP = mean arterial pressure; Hct = haematocrit; APACHE: acute physiology and chronic health examination; GCS = Glasgow coma scale; CHS = chronic health score; SOFA = sequential organ failure assessment; SIRS = systemic inflammatory response syndrome; POP = pancreatitis outcome prediction; BMI = body mass index; BISAP = bedside index for severity in acute pancreatitis; CRP = C-reactive protein; HAPS = harmless acute pancreatitis score.

and/or as a mean to monitor the early resuscitation treatment, with the exception of patients with known chronic renal insufficiency. On the other hand, renal function is a basic parameter of almost all multifactorial scoring systems for prognostic assessment of patients suffering from AP.

## MULTIFACTORIAL PROGNOSTIC SCORING SYSTEMS

Over the last few decades, many multifactorial prognostic systems in AP have been proposed (Table 3-II). Available scoring systems incorporate physiologic, laboratory, and occasionally radiographic parameters, and, in general, they have been shown to perform with only moderate overall sensitivity but high negative predictive value.<sup>3, 9, 13</sup> Suboptimal values for positive predictive power (proportion of predicted severe attacks which proved to be severe) were observed considering as severe outcome both local/systemic complications and mortality.<sup>4</sup> The predictive accuracy may be limited by the use of cut-off values and the conversion of continuous variables into binary values of equal prognostic weight, which fail to capture any potential synergistic or multiplicative effects of these parameters.<sup>5</sup> Moreover, the studies in which each prognostic score was validated associate all types of organ failure as se-

vere outcome of AP without any difference between transient and persistent organ failure. The latter, defined as organ failure lasting for 48 hours and involving the cardiovascular, pulmonary, and/or renal systems, has increasingly become recognized as the most clinically relevant indicator of disease severity, directly associated with both the risk of local complications and death.<sup>14</sup> Many studies that introduced or assessed these multifactorial clinical scoring systems present an important limitation relative to the small number of enrolled patients with severe AP. Lastly, the paucity of comparative studies limits our understanding on the accuracy of these prognostic systems. Despite its several limitations, the most widely used multi-parametric prognostic score is the APACHE II score.<sup>15</sup> This score was initially designed as an intensive care unit instrument and therefore requires the collection of a large number of variables, some of which may not be relevant to prognosis in AP. The chronic health-profile portion of the score requires knowledge of patient history and medication details, which may not be available if the patient is unconscious, intubated, or transferred from an outside hospital with few medical records. The APACHE II score is also clinically cumbersome and difficult to remember for clinicians. The main advantage is that it can be calculated on admission and thereafter on a daily base,



while the Ranson and Glasgow scoring systems take 48 hours from admission. Addition of a score for obesity based upon values of the body mass index (the so-called APACHE-O) increases the predictive accuracy and positive predictive values for severity.<sup>16</sup> BISAP (*bedside index for severity in acute pancreatitis*) score<sup>17</sup> is easier to calculate, requires only those vital signs, laboratories, and imaging that are commonly obtained at onset or within 24 h of presentation and seems to be able to predict in-hospital mortality with higher accuracy than the other recent multi-parametric scores. Otherwise, the accuracy in prediction of persistent organ failure is quite similar for all multifactorial score listed in table II: positive predictive values ranging from 34% for Panc-3 score to 61% for APACHE-II by using data at admission.<sup>5</sup> Considering all these features, none of the multifactorial prognostic systems is fully satisfying. Combination of predictive scores may prove reasonably more accurate than each single scoring system, but this is quite unsuitable in a clinical setting.

## RADIOLOGIC PROGNOSTIC SCORING SYSTEMS

Computed tomography-scan (CT) represents a valuable method to identify pancreatic necrosis. Based upon this feature and upon the notion that necrotizing pancreatitis is more likely to associate with a severe clinical outcome, many prognostic scoring systems by using CT features were proposed (Table 3-III). The first potential bias we have to consider when faced with these imaging scoring systems is related to the fact that only two out of eight listed in Table 3-III are based on CT scan

features were obtained with intravenous bolus-injection of contrast medium. Contrast-enhanced CT-scan is currently the gold standard in identification of pancreatic necrosis and its quantification (perfused and non-perfused tissue in and around the pancreas represent vital and necrotic tissue, respectively). Another weak point to consider is that, despite the positive correlations to morbidity and mortality of the several imaging scoring systems, the *interval between admission and radiologic scoring* remains relatively long and even longer between onset and scoring. Predictive scoring systems are only of value when they can predict an event before it happens, which allows time for intervention. For all scoring systems listed in Table 3-III, a time interval ranging between 24 hours and 10 days after admission was reported.<sup>18</sup> For example, the initial Balthazar score in 1985 was derived from CT images obtained within 10 days of hospitalization and in 2004 from CT images obtained within 72 hours of admission.<sup>19</sup> The pilot study of CTSI (*computed tomography severity index*) was established with a CT performed within 7 days of admission and most studies of validation of this index are based on a CT scan performed within 72 hours of admission, when necrosis is fully accomplished.<sup>20</sup> As concerns the PSI (*pancreatic size index*), CT scans were performed within 48-72 hours from admission, whereas the EPIC (*extra-pancreatic inflammation on CT*) index score or EP (*extra-pancreatic*) score was calculated within 24 h of admission.<sup>18</sup> A scoring system derived from CT images obtained within 10 days of admission may have a high predictive value for disease severity and mortality. Nevertheless, only the prediction of mortality will

**Table 3-III** Computed tomography scan scoring systems (bibliography of each score can be founded in references<sup>3-6, 18-20</sup>).

CT scoring system	Year	i.v. contrast agent	Parameters
Original Balthazar scoring system	1985	No	Extent of pancreatic and peripancreatic inflammatory changes
EP	1985	No	Extrapancreatic complications
PSI	1989	No	Size of pancreas
CTSI	1990	Yes	Quantification of extrapancreatic inflammation and the extent of pancreatic necrosis
MOP	2003	No	Mesenteric oedema and peritoneal fluid
Modified CTSI	2004	Yes	CTSI + extrapancreatic complications (vascular, gastrointestinal, pleural effusion, ascites)
EPIC	2007	No	Extrapancreatic inflammation (pleural effusion, ascites, retroperitoneal fluid collections)

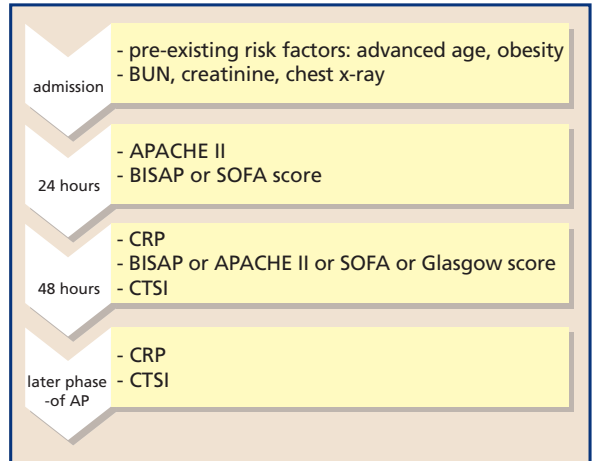
CT = computed tomography; i.v. = *intra-venous*; EP = extrapancreatic score; PSI = pancreatic size index; CTSI = computed tomography severity index; MOP = mesenteric oedema and peritoneal fluid index; EPIC = extrapancreatic inflammation on CT index.

have clinical value because the severity prediction is too late in the natural course of disease, as it is already present at that time. Although sensitivity and specificity are important parameters of the potential of a score, they can easily be manipulated by using different cut-off values of the test. The overall performance of a test is more accurately represented by the area under the curve of the receiver operating characteristics (ROC) curve with relative 95% confidence interval.<sup>9</sup> But, at present, only the EPIC score and the MOP (*mesenteric oedema and peritoneal fluid*) index are supported by ROC curves.<sup>18-20</sup>

In conclusion, imaging techniques should be used for mortality prediction by the above-cited scoring systems and as therapeutic guidance rather than as early-risk stratification tool, as nonspecific illness scoring systems like BISAP and APACHE II seem to be more acceptable at the bedside for risk stratification within the first 24 h.

## WHAT SHOULD WE DO IN CLINICAL PRACTICE?

Based on the above considerations, we should rationally utilise different prognostic scores in relation to the different phases of AP to obtain a reliable identification of patients who are at risk to develop major complications or fatal outcome. To reach this target we must optimize the clinical application of currently available risk factors, markers of severity and scoring systems bearing in mind that clinical scoring systems accurately correlate with systemic complications and mortality, but radiologic scoring systems diagnose clinically severe disease more accurately and better correlate with pancreatic infection and the need for intervention. Figure 3.1 illustrates our proposal for a step-by-step prediction of AP severity, based upon our experience and current clinical practice not forgetting the above-discussed points of strength and weakness of the most widely diffuse prognostic methods. At admission, identification of pre-existing risk factors such as obesity and advanced age together with simple laboratory data (BUN, creatinine) and chest-x-ray enables us to discriminate, with enough reliability, AP patients with mild forms. At 24 hours from admission, assessment of patients with a multifactorial scoring system such as APACHE II, BISAP or SOFA is necessary to identify patients who are at risk for organ failure (we personally prefer the BISAP score for its simplicity). At 48 hours,



**Figure 3.1** Proposal of a step-by-step prediction of severity in acute pancreatitis. (BUN = blood urea nitrogen, BISAP = bedside index for severity in acute pancreatitis; SOFA= sequential organ failure assessment; CRP = C-reactive protein; CTSI = computed tomography severity index; AP = acute pancreatitis).

this group of patients must be investigated with the same prognostic score chosen at 24 hours plus CRP and a radiologic score as CTSI. Subsequently, monitoring should be based on CRP values, one organ failure score and repetition of contrast-enhanced CT scan to evaluate the occurrence of complications and the variation in the extent of pancreatic necrosis/peripancreatic fluid collections.

In clinical practice it is important to identify patients with AP who are at risk of developing persistent organ failure early in the course of disease. Regular clinical review and timely intervention remains the mainstay of treatment in order to identify deterioration of the disease.

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# HOW TO MANAGE LOCAL COMPLICATIONS: THE ROLE OF ENDOSCOPY

## 6

T.H. Baron

ERCP and endoscopic ultrasound (EUS) for treatment of pancreatic disease continues to evolve. Endoscopic therapy is useful for the treatment of pancreatic diseases including local complications of the acute and chronic pancreatitis, which will be reviewed in this chapter.

### LOCAL COMPLICATIONS OF ACUTE PANCREATITIS

Several types of pancreatic and peripancreatic fluid collections may arise as a result of acute pancreatitis. These include acute fluid collections, acute pancreatic pseudocysts, walled-off pancreatic necrosis (WOPN, formerly organized pancreatic necrosis, OPN) and, pancreatic abscesses.<sup>1</sup>

Acute fluid collections form early in the course of acute pancreatitis (before 4 weeks) and usually resolve without therapy. They are peripancreatic and contain no solid debris. Rarely acute fluid collections rapidly enlarge causing local compressive symptoms and/or become infected, and require drainage.

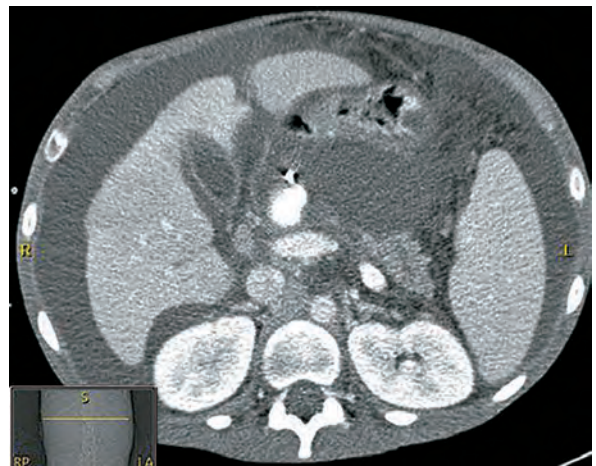
Acute pseudocysts arise as a sequela of acute pancreatitis, require at least four weeks to form, and are devoid of significant solid debris. The mechanism of formation of an acute pancreatic pseudocyst is usually as a result of limited pancreatic necrosis that produces a pancreatic ductal leak. Alternatively, areas of pancreatic and peripancreatic fat necrosis may completely liquefy over time and become a pseudocyst. Despite the requirement of at least 4 weeks for a pseudocyst to form, it is important to realize that some patients with significant pancreatic necrosis (>30%) may evolve the early acute pancreatic necrosis and peripancreatic necrosis into a collection that radiographically resembles a pseudocyst.<sup>2, 3</sup> These collections contain

significant solid debris and endoscopic treatment using typical pseudocyst drainage methods results in infectious complications because of contamination and inadequate removal of solid debris.<sup>4</sup>

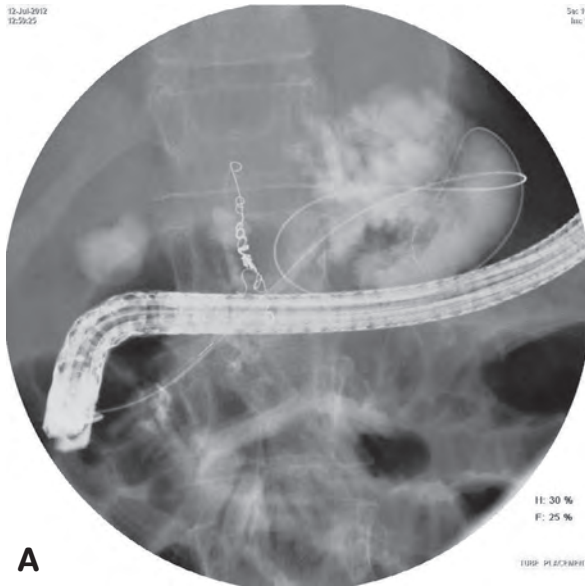
### ENDOSCOPIC TREATMENT OF LOCAL COMPLICATIONS OF ACUTE PANCREATITIS

#### *Acute pancreatic pseudocysts*

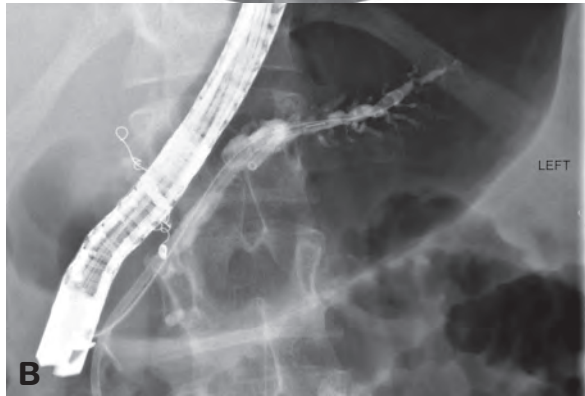
Pseudocyst drainage is indicated for treatment of symptoms and/or infection<sup>5</sup> and progressive enlargement on imaging studies. Symptoms due to an acute pseudocyst include abdominal pain - often exacerbated by eating, weight loss, gastric outlet obstruction, obstructive jaundice, and pancreatic duct leakage. Pancreatic duct leakage may result in pancreatic ascites (Figure 6.1) or pancreatic fistulae.<sup>6</sup> Pseudocysts



**Figure 6.1** Abdominal CT of patient with chronic alcoholic pancreatitis, pancreatic pseudocyst, and documented pancreatic ascites.



A



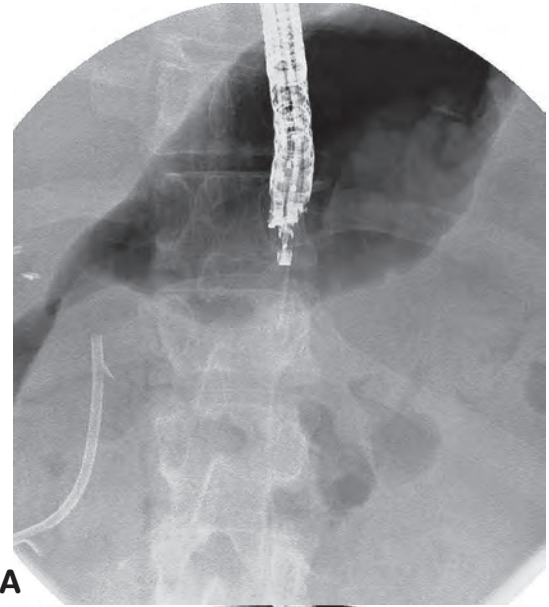
B

**Figure 6.2** Endoscopic transpapillary therapy of patient. A) Contrast injection through the main pancreatic duct (PD) into pancreatic pseudocyst. A 7 Fr stent was placed into the cavity. B) Follow-up pancreatogram shows stent in residual cavity; the duct was successfully reconnected. The pseudocyst and ascites resolved.

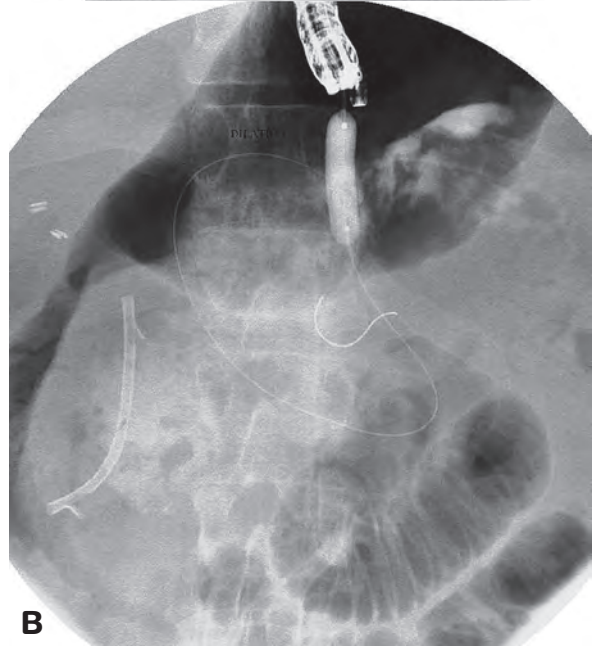
may be drained through the papilla (transpapillary), through the gastric or duodenal wall (transmurally), or using a combination of the two.

**Transpapillary drainage**

If the pseudocyst communicates with the main pancreatic duct, placement of a pancreatic duct stent with or without pancreatic sphincterotomy is effective, especially for smaller pseudocysts (<5-6 cm) that are not otherwise approachable transmurally.<sup>7</sup> The proximal end of the stent (toward the pancreatic tail) may directly enter the pseudocyst (Figure 6.2), bridge the area of leak into the pancreatic duct upstream from the leak, or lie



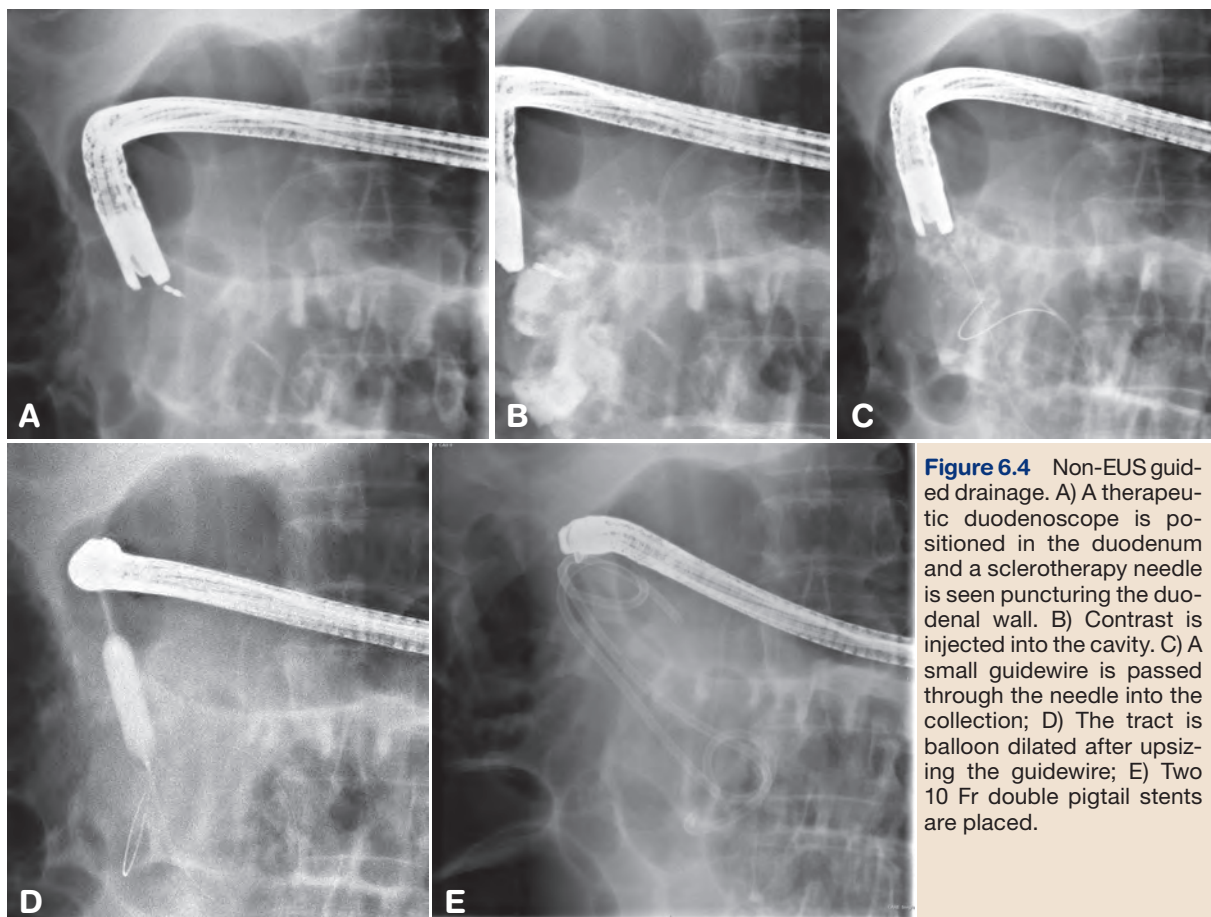
A



B

**Figure 6.3** EUS-guided drainage of walled-off pancreatic necrosis. A) Therapeutic channel echoendoscope is positioned in stomach and 19-gauge needle can be seen puncturing into gastric wall. B) Guidewire has been passed through wire and coiled into collection. A dilating balloon is inflated across the gastric wall.

completely downstream to the leak. Bridging the leak is the preferred approach since it restores ductal continuity and appears to be more effective.<sup>8, 9, 10</sup> Transpapillary drainage avoids bleeding or perforation that may occur with transmural drainage. However, pancreatic stents may induce scarring of the main pancreatic duct.<sup>11</sup>



**Figure 6.4** Non-EUS guided drainage. A) A therapeutic duodenoscope is positioned in the duodenum and a sclerotherapy needle is seen puncturing the duodenal wall. B) Contrast is injected into the cavity. C) A small guidewire is passed through the needle into the collection; D) The tract is balloon dilated after upsizing the guidewire; E) Two 10 Fr double pigtail stents are placed.

### Transmural drainage

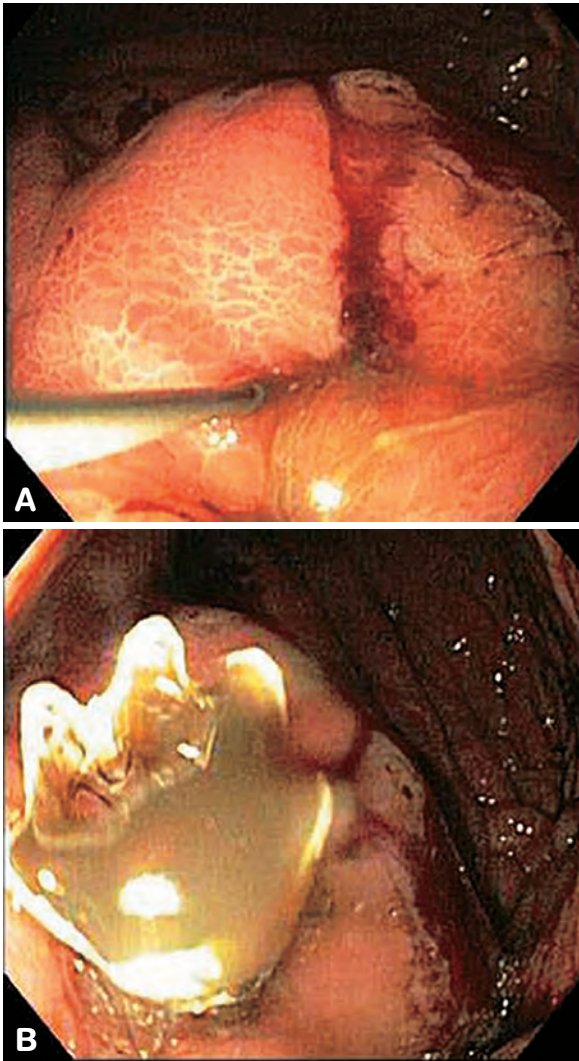
There is no standardized approach to transmural pseudocyst drainage. Transmural drainage is performed by entering the cyst using a needle without cautery or using a cautery device (e.g., needle knife), with EUS (Figure 6.3) or without EUS (Figure 6.4). Some endoscopists feel EUS-guided drainage is mandatory prior to performing endoscopic transmural drainage to prevent bleeding and perforation.<sup>10, 12</sup> Although the superiority of EUS-guided *vs* non EUS-guided drainage has not been clearly demonstrated,<sup>13</sup> there is increasing data to support its routine use during transmural drainage,<sup>13-15</sup> especially when non-EUS guided drainage fails.<sup>16</sup> EUS-guided entry is successful in more than 95% of patients and with low complication rates.<sup>17-19</sup> A variety of EUS techniques can be used.<sup>20</sup>

Non-EUS-guided entry can also be performed<sup>21</sup> and in the hands of experienced operators successful transmural entry has been reported in 91/94

patients in lesions as small as 3 cm and without endoscopically visible extrinsic compression (Figure 6.4).<sup>22</sup> Once the pseudocyst is successfully entered the transmural tract is balloon dilated to 8-10 mm in diameter to allow placement of one or two 10 Fr stents.<sup>23</sup>

Alternatively, transmural placement of a covered, removable single self-expandable metal biliary stent can be used (Figure 6.5).<sup>24, 25</sup> This is particularly advantageous when using an echoendoscope as the smaller stent delivery system allows drainage with minimal dilation and only one stent placement.

Following uncomplicated attempted endoscopic drainage a follow-up CT scan is obtained 4-6 weeks after the drainage procedure. The internal stents are endoscopically removed after documented radiographic resolution. Success rates, recurrence rates and complication rates of endoscopic drainage of pancreatic pseudocysts are variable, likely because of many reports included acute and chronic pseudocysts and pancreatic abscesses. In



**Figure 6.5** Placement of fully covered self-expandable metal stent (SEMS) into pancreatic fluid collection. A) The proximal gastric wall has been punctured and guidewire passed into collection. B) Immediately after deployment of SEMS.

addition, some patients underwent transpapillary drainage while others transmural drainage. Nonetheless, cumulatively successful drainage is achieved in approximately 75-90% with complication rates of about 5-10% and recurrence rates of 5-20%.<sup>26, 27</sup>

### **ORGANIZED PANCREATIC NECROSIS (WALLED-OFF PANCREATIC NECROSIS)**

Pancreatic necrosis is nonviable pancreatic parenchyma usually with peripancreatic fat necrosis.



**Figure 6.6** Coronal view of abdomen / pelvis shows extensive organized pancreatic necrosis. Due to gastric outlet obstruction endoscopic necrosectomy was performed and after multiple procedures resolved.

In the earliest form, this is detected on contrast enhanced CT by the presence of non-enhancing pancreatic parenchyma. Pancreatic necrosis is frequently accompanied by major pancreatic ductal disruptions. Over the course of several weeks, the collection may continue to evolve and expand the initial area of necrosis and contains both liquid and solid debris (Figure 6.6). The terms organized pancreatic necrosis<sup>6</sup> and walled off pancreatic necrosis (WOPN)<sup>4</sup> have been used to differentiate this process from the early (acute phase) of pancreatic necrosis. The CT appearance of organized pancreatic necrosis may be mistaken as an acute pseudocyst.<sup>2</sup>

The indications for and timing of drainage of sterile WOPN are controversial. Endoscopic drainage cannot be performed until the process becomes organized, which usually occurs several weeks after onset of pancreatitis. Indications for drainage of sterile WOPN are refractory abdominal pain, gastric outlet obstruction or failure to thrive (continued systemic illness, anorexia, and weight loss) at 4 or more weeks after the onset of acute pancreatitis. Since endoscopic drainage of WOPN is more technically difficult, carries a higher rate of complications, and tends to involve a more severely ill pa-