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# Advances in management of pancreatic necrosis

## Introduction and pathophysiology

An increasing incidence of acute pancreatitis has been reported recently, with an estimated 21,000 new cases per year in the United States.[1] On the one hand, most of these cases are the mild form of pancreatitis with an expected complete recovery. On the other hand, severe acute pancreatitis (SAP) is associated with increased morbidity and mortality. Overall, 20% of SAP cases are due to a necrotizing process.[2] The addition of infection further increases the overall mortality rate.

The causes for acute pancreatitis are well recognized. Gallstones and alcohol take the lead as the biggest offenders. The pathophysiology behind acute pancreatitis, on the contrary, is not well understood.[3] Although the initial insults are still debated, the cascades of molecular events leading to the pancreatitis picture is being unraveled; Intracellular activation of digestive enzymes are believed to be a key factor in the process of pancreatitis, along with the release of inflammatory cytokines and vascular compromise.[3] Cellular stress resulting from the initial offense leads to liberation of reactive oxygen radicals within the cell and impaired transport of zymogens across the cellular membrane. Intracellular zymogens then fuse with lysosomes, resulting in activation of trypsinogen through lysosomal protease cathepsin B. This results in autocellular digestion, inflammation, and tissue necrosis.[3] Lipase and amylase leak occurs because of an increased permeability of pancreatic duct or basolateral secretion; this leads to the known increased serum level in acute pancreatitis attack. However, these leaking pancreatic enzymes are not linked to further inflammatory processes.[4] Instead, it is the immune system that triggers a sequence of inflammatory signals, leading to further damage and cellular necrosis. When pancreatic cells are injured owing to premature activation of trypsinogen, high mobility group box protein 1 is released and is responsible for creating further inflammation mediated through toll-like receptor 4, serving as damage-associated molecular patterns. The result of this pathway is activation of caspase 1 and the release of interleukins (IL), IL-1 and IL-18. The release of these mediators leads to a state of inflammation and further cellular damage.[4] It could be speculated that genetic and environmental factors affect the magnitude of this inflammatory cascade. This may result in these extrinsic factors having a significant role in determining the severity of acute pancreatitis and development of pancreatic necrosis. The role of tissue necrosis factor (TNF)-$\alpha$ in the cascade has been studied as well and although no causative relationship has been identified between TNF-$\alpha$ and development of acute pancreatitis, it is believed that TNF-$\alpha$ enhances the ongoing inflammatory response, leading to the systemic inflammatory

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response syndrome (SIRS).[5] TNF-$\alpha$ is a common pathway in distress signaling and may in itself not cause the injury, but may be the signal for downstream injury activation.[5-7]

The immunomodulatory cytokine, IL-10, has been postulated to decrease inflammation in acute pancreatitis.[8] The sonic hedgehog protein has been the topic of much research in pancreatic disease and may have a role in augmenting IL-10 response to injury.

*Biliary pancreatitis*

The pathophysiology of biliary pancreatitis has been investigated since the mid-19th century. In early 1990s, Eugene Lindsay Opie published 2 hypotheses addressing the initial insults of gall bladder stones leading to development of pancreatitis. The impaired outflow hypothesis was published when Opie reported the presence of impacted gallstones at the ampulla, which was found during the autopsy of 2 patients with acute pancreatitis.[9] This hypothesis was later validated in animal models where pancreatitis is induced as a result of ligation of pancreatic duct. The increase in pancreatic duct pressure, ductal hypertension, seems to result in cellular distress initiating the cascade of molecular events, leading to the pancreatitis picture. Opie then published a second report hypothesizing reflux of bile content into the pancreatic duct as an explanation for acute biliary pancreatitis.[10] This has been named the common channel hypothesis. This hypothesis, along with hypothesis of duodenal reflux into the pancreatic duct, has been heavily disputed since then. A recent finding is that patients after sphincterotomy appear not to be at a higher incidence of pancreatitis, despite presumed reflux of duodenal contents into the pancreatic duct.[10] Although not fully understood, it seems that Opie's hypothesis of ductal hypertension, first published in 1901, still stands strong as the likely explanation of biliary pancreatitis at this time.

*Alcoholic pancreatitis*

Alcohol-induced pancreatitis has been studied heavily under the hypothesis of direct toxicity to the pancreas or through enhancing the effect of other pancreatitis-inducing factors. The relationship between alcohol consumption and development of pancreatitis is not well understood. Most patients with acute pancreatitis report a history of alcohol consumption but fewer than 10% of heavy alcohol consumers develop acute pancreatitis.[11] Furthermore, no threshold for the time or amount of alcohol consumption has been identified to cause pancreatic damage.[3] This is explained by the notion that alcohol-induced pancreatitis is a multifactorial process where genetics and environmental factors play considerable roles in its pathogenesis. Effectively, like in many diseases, it appears that there must to be a “2-hit” phenomenon for acute pancreatitis to develop in the patient that drinks alcohol. When alcohol is linked to pancreatitis, it is identified as a risk factor for developing necrotizing disease.[12] Many studies have investigated multiple potential pathogenesis of cell death in alcohol pancreatitis. A potential route is intracellular activation of digestive enzymes, namely expression and activation of cathepsin B[3]. Alcohol is also thought to affect inflammatory signaling pathways and the activity of caspases leading to tissue necrosis. The pancreas was also found to metabolize ethanol into fatty acid ethyl esters, which are thought to result in increased intracellular calcium concentration. Increased intracellular calcium can lead to activation of intracellular enzymes, resulting in cellular injury, cell death, and pancreatic necrosis. In summary, it appears that alcohol in itself is not enough to cause pancreatitis. A second hit is necessary, likely a genetic predisposition to pancreatitis. The end result is that pancreatitis caused by alcohol involves activation of intracellular cathepsin B and caspases, leading to autodigestion and injury.

*Endoscopic retrograde cholangiopancreatography–related pancreatitis*

Pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP) occurs in 2%-9% of cases.[13] The mechanisms contributing to the pathophysiology of acute pancreatitis after ERCP

are attributed to increased pancreatic ductal pressure or direct toxicity from injected contrast material.[14] Pancreatic sphincter injury, edema, and spasm during or after ERCP, and excessive contrast injection into the pancreatic duct are believed to cause pancreatic ductal hypertension.[15] In many ways, this is reminiscent of Opie's theory of pancreatitis. Sphincter of Oddi dysfunction, age younger than 60 years, normal bilirubin level, and a history of ERCP-related pancreatitis have been identified as patient-related risk factors associated with an increased risk of pancreatitis after ERCP.[15] Effectively, patients with a normal gland or a “finicky gland” are at risk for pancreatitis after ERCP.

This entity has been difficult to study as many patients undergoing ERCP have had pancreatic pathology as the reason for the study or have a history of pancreatic or biliary disease. The role of sphincter dysfunction and prevention of pancreatitis after ERCP has been a topic of much study. The placement of a pancreatic ductal stent, allowing for drainage of the pancreatic duct, has been shown to decrease pancreatitis after ERCP.[16] Pretreatment with rectal nonsteroidal anti-inflammatory drugs has also been associated with a decrease in pancreatitis in this setting.[17]

## Definitions and terminology

The importance of adequate classification of pancreatitis and its severity was recognized as early as the 19th century. The first attempt at such classification was by Fitz in 1889.[18] Fitz's classification of severity was based on the presence of hemorrhage or necrosis. The next significant modification did not happen until 1992 in Atlanta at the international symposium on acute pancreatitis.[19] As with Fitz's classification, the Atlanta classification was based primarily on morphologic features of pancreatic necrosis, abscess, or pseudocyst. The original Atlanta classification was mainly an imaging-based diagnostic scheme. Since its original iteration, there has been an ongoing effort to update and revise the classification to enhance its compatibility with clinical practice.[18] In recent years, the Atlanta classification of acute pancreatitis was considered inadequate by a significant portion of practitioners.[20] This has led to a new revised classification of acute pancreatitis in 2012 adopting local and systemic factors as the basis for the classification.[21] The main aim of the newer terminology and classification is to accurately describe the imaging findings and clinical presentation of acute pancreatitis. The classification attempts to place patients into categories that help outline the expected clinical course for that patient.

There are 2 types of acute pancreatitis recognized in the 2012 revised Atlanta classification: (1) interstitial edematous pancreatitis and (2) necrotizing pancreatitis.

Interstitial pancreatitis is defined by the lack of pancreatic or peripancreatic necrosis on imaging (Fig 1). It could be either diffuse in nature involving the whole gland or localized to a portion of the pancreas. This type constitutes the overwhelming majority of acute pancreatitis

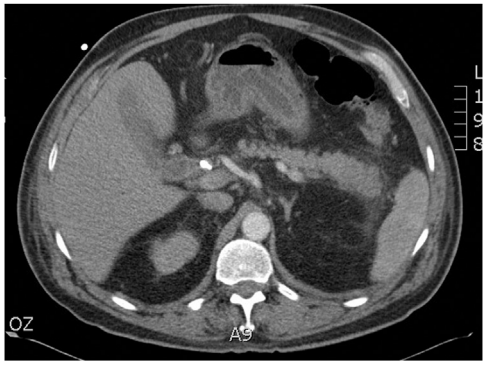

**Fig. 1.** Enhanced CT scan of interstitial pancreatitis involving the tail of the pancreas.

(80%-90%) and is usually self-limiting, commonly resolving within a week. The concept is that there is injury to the gland that has resulted in edema and autodigestion without necrosis of the tissue. The pancreas can appear boggy and swollen with rounded edges and adjacent fluid. However, there is no lack of perfusion of the gland, as seen in necrotizing pancreatitis.

Contrarily, necrotizing pancreatitis occurs in 10%-20% of cases of acute pancreatitis and is defined by the presence of necrosis either within the pancreatic parenchyma itself or in the peripancreatic tissues (Fig 2). Necrotizing pancreatitis is further classified as parenchymal necrosis alone, peripancreatic tissue necrosis, or both. Peripancreatic necrosis without parenchymal necrosis is believed to be a separate entity with potentially fewer complications.[22] In these cases of necrosis, there may be edema associated with the gland, together with fluid collections. There is generally a disruption in the gland where there is an area of necrosis. This is best seen on a contrasted computed tomography (CT) scan.

The revised Atlanta criteria then looked at the severity of pancreatitis. This grading was intended to aid the treating physician in identifying the severity of illness, help with prognostic factors, and potentially evaluate for the need for transfer to a higher level of care. The severity of acute pancreatitis is categorized into 3 degrees: (1) mild, (2) moderately severe, and (3) severe.

The level of severity is determined based on the presence of persistence of organ failure, local complications, and systemic complications. The 2012 revised classification recognized 2 types of organ failure: transient organ failure that resolves within 48 hours and persistent organ failure lasting more than 48 hours. Mild acute pancreatitis is defined by the lack of organ failure, local complications, or systemic complications. Moderately SAP is defined by the presence of transient organ failure or the presence of local or systemic complications without persistent organ failure or both. The third degree of severity is SAP. This is characterized by the presence of persistent organ failure, involving single or multiple organs. It is our belief that the addition of local and systemic complications to the definition of the degree of severity would help its translation into clinical practice and create a common language among practitioners dealing with acute pancreatitis. The revised Atlanta criteria aid the clinician in triaging patients with acute pancreatitis into 3 groups based on the severity of clinical presentation. This can help identify those patients that have the potential to require resources that may not be available at every hospital.

The next area of focus in the revised criteria is based on imaging. Dedicated pancreas protocol CT is the imaging test of choice to stratify fluid collections correctly in patients with SAP. Pancreatic and peripancreatic fluid collections are defined in the 2012 revised classification based on morphology and timing in the course of the disease. Four types of collections are identified: (1) acute peripancreatic fluid collection, (2) pancreatic pseudocyst, (3) acute necrotic collection, and (4) walled-off pancreatic necrosis (WOPN).

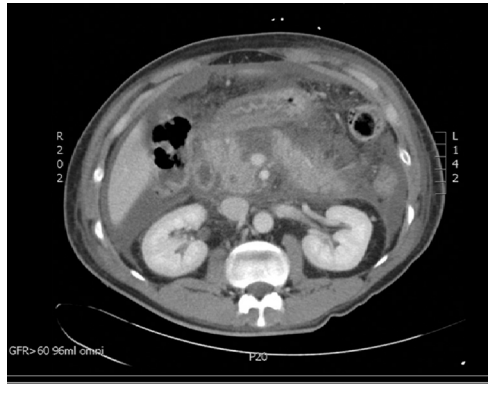


**Fig. 2.** Enhanced CT scan of necrotizing pancreatitis.

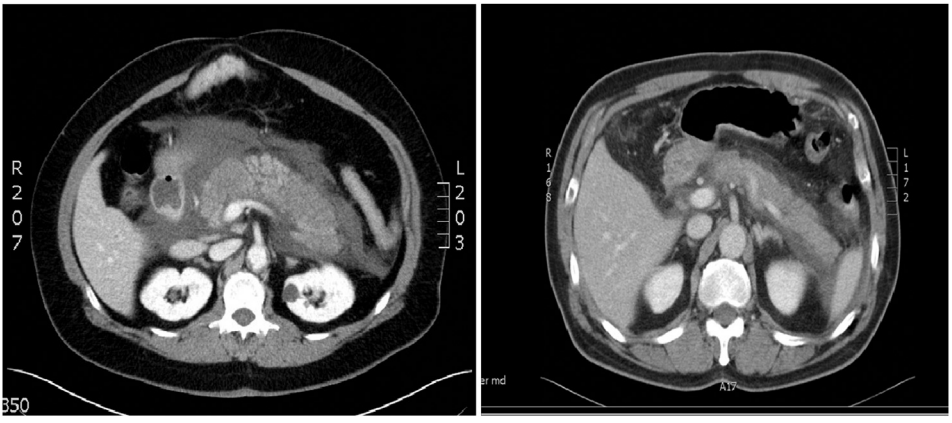


**Fig. 3.** Enhanced CT scan of acute peripancreatic fluid collection.

An acute peripancreatic fluid collection is characterized by the lack of a well-defined wall and is confined by the normal fascial planes of the retroperitoneum (Fig 3). This fluid collection occurs in the early stage of interstitial acute pancreatitis, usually the first 1-3 weeks, and remains sterile. These collections commonly resolve without intervention. In this circumstance, the fluid tracks into spaces in the lesser sac and the collection has angulated, fingerlike edges. There is no mass effect of adjacent structures.

Pancreatic pseudocysts are the result of a persistent acute peripancreatic collection beyond 4 weeks. They are characterized by the presence of a well-defined wall (Fig 4). Pancreatic pseudocysts should display mass effect on adjacent structures, the stomach being the most commonly affected structure. The presence of jagged edges and projections, rather than rounded edges, is more suggestive of acute peripancreatic collection than pseudocyst. Of importance is that pancreatic pseudocysts only arise in interstitial pancreatitis and not necrotizing pancreatitis. This is a change from older terminology, where any fluid collection in the delayed period was called a pseudocyst. Owing to the fact that pseudocysts are mature compared with acute peripancreatic fluid collections, which by definition arise in interstitial pancreatitis, pseudocysts are not associated with pancreatic necrosis and have no solid material within their

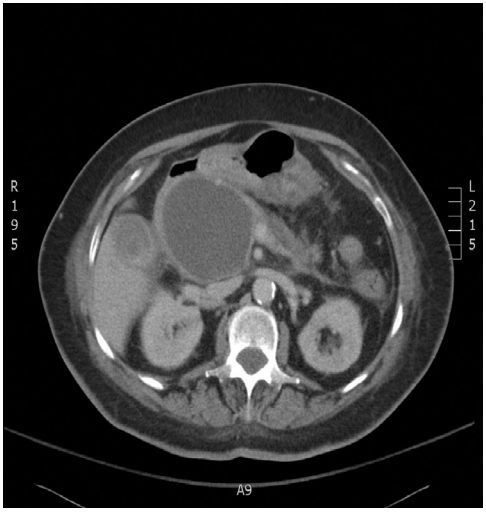


**Fig. 4.** CT image of pancreatic pseudocyst.

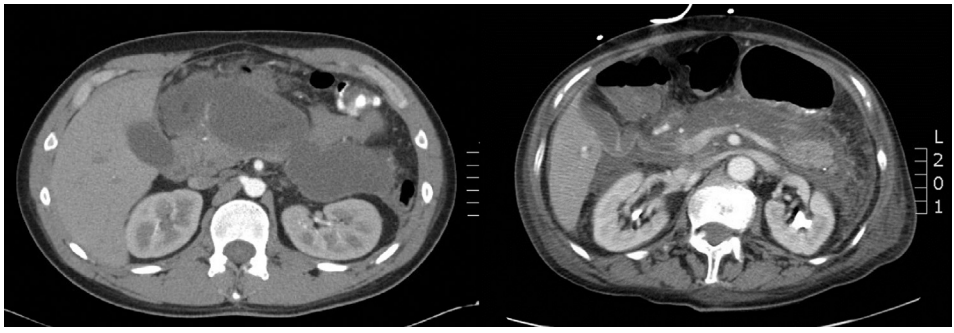

**Fig. 5.** Enhanced CT scan shows acute necrotic collections.

substance. In this sense, true pancreatic pseudocysts are extremely rare. The imaging of a pseudocyst should show a fluid collection, causing mass effect to adjacent structures, and should contain no necrotic material within it.

Acute necrotic collections take place within the first 4 weeks of the disease and contain variable amounts of fluid and necrotic solid materials (Fig 5). As compared with pancreatic pseudocyst that occurs in interstitial pancreatitis, by definition, acute necrotic collection is associated with necrotizing pancreatitis. Differentiation between acute peripancreatic fluid collection and acute necrotic collection can be challenging on imaging in the first few days of acute pancreatitis. As the presence of necrosis evolves with time, the presence of solid materials on imaging becomes more evident, aiding the identification of this type of collection. When acute necrotic collection persists beyond 4 weeks, they become encapsulated and the term walled-off pancreatic necrosis (WOPN) is used (Fig 6). WOPN refers to a collection that expresses mass effect on adjacent structures, but contains solid material as well as fluid. The timing of WOPN is usually in the late phase (greater than 4 weeks). Again, pancreatic pseudocyst should contain no necrotic material, whereas WOPN contains fluid and necrosis.

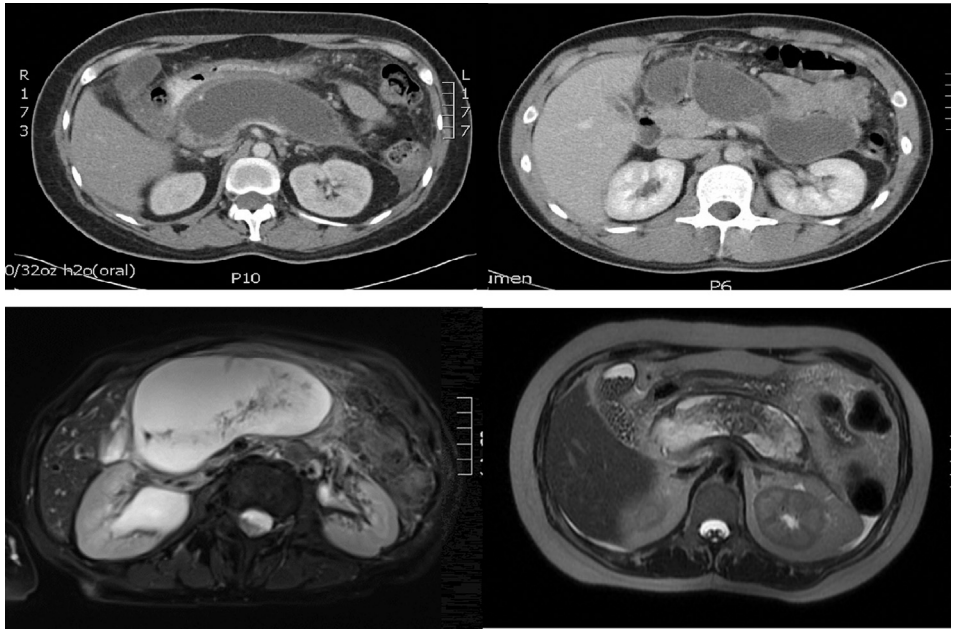

**Fig. 6.** Walled-off pancreatic necrosis on enhanced CT (upper panels) and T2-weighted MRI (lower panels).

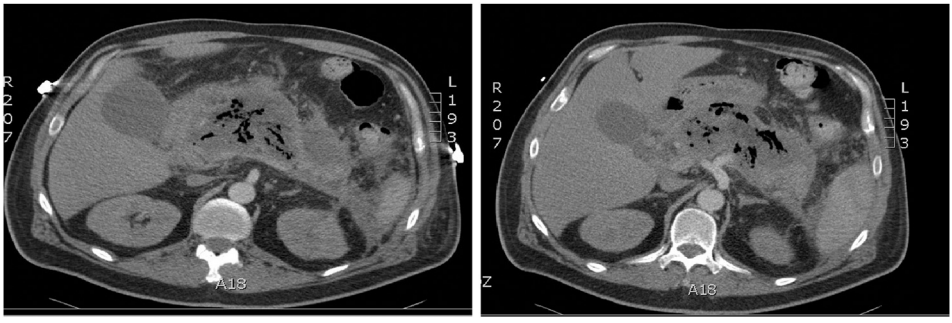


**Fig. 7.** Enhanced CT scan of infected pancreatic necrosis shows extraluminal gas within pancreatic collection.

The new classification also addresses the presence of infected vs sterile necrosis. The presence of infected necrosis is diagnosed based on 1 of 3 criteria: (1) ongoing signs of sepsis or the combination of clinical signs or both and the CT finding of extraluminal gas within areas of necrosis (Fig 7); (2) percutaneous, image-guided fine-needle aspiration (FNA) when bacteria or fungi or both are seen on Gram stain and the culture is positive; or (3) as a secondary event after instrumentation.

The revised criteria attempt to include both radiographic and clinical indicators to arrive at a definition that is useful for the clinician. It is noteworthy that the finding of infected pancreatic necrosis can be made without documentation of infection. Air within the fluid collection is assumed to represent infection. In our experience, air within a pancreatic fluid collection (PFC) often means that a fistula to adjacent bowel has occurred. The treating physician must be aware of this possibility.

## Clinical diagnosis and assessment of severity

The diagnosis of acute pancreatitis is usually straightforward with patients presenting to the emergency department with acute onset of upper abdominal pain. The presence of 2 of the 3 following criteria is sufficient to diagnose acute pancreatitis[21]: (1) clinical criteria—acute upper abdominal pain, the classic description of radiating pain to the back is frequently present as well; (2) laboratory criteria—amylase or lipase serum level greater than 3 times the upper normal limit; and (3) imaging criteria—CT findings consistent with the diagnosis of acute pancreatitis.

In patients presenting within 24 hours of the onset of their symptoms, the presence of elevated lipase or amylase level on admission is detected with a sensitivity of 98%.[14] The level of pancreatic enzyme frequently normalizes within 5-7 days even in the presence of pancreatic necrosis.[14] A CT scan is usually not required on presentation unless it is needed to rule out other potential differential diagnoses. Most cases of acute pancreatitis are mild in nature and resolve spontaneously within the first week and a CT scan is rarely required in such scenarios. In cases of severe pancreatitis, enhanced CT is the diagnostic modality of choice to assess the morphologic features of the inflamed gland and to identify pancreatic necrosis.

When acute pancreatitis is diagnosed, identification of its etiology should be attempted. An ultrasound (US) image of the right upper quadrant may visualize gall bladder stones or sludge in biliary pancreatitis cases. Laboratory values can be important in determining the etiology as well; an increase in the alanine aminotransferase level to greater than 60 U/L is associated with the etiology of acute pancreatitis being of biliary source.[23] Other more unusual etiologies of pancreatitis, such as hypertriglyceride-related pancreatitis, can be evaluated by checking the triglyceride levels, calcium levels, etc.

Mild acute pancreatitis cases have an expected complete recovery within 1 week with a mortality rate of less than 1%. On the contrary, severe pancreatitis has a mortality rate of

10%-30%.[24] Pancreatic necrosis occurs in 20% of cases of acute pancreatitis, with 30% of these cases developing pancreatic infection, which further affects the morbidity and mortality of the disease.[2] Assessment of the severity of the attack and predicting the course of the disease are important when determining the allocation of care for these patients or the need for transfer to a higher level care early in the disease process.

Two stages have been identified in the course of acute pancreatitis. Stage 1 occurs in the first 2 weeks. The clinical manifestations of acute pancreatitis during this phase are the result of cytokines release which may produce a SIRS picture. When death occurs in this phase, it is usually secondary to SIRS and multiorgan failure. Stage 2 takes place after 2 weeks. Development of infection and local complication of pancreatic necrosis occur in this phase. Multiorgan failure due to sepsis and infection plays a major role in determining the mortality during this phase.

The Atlanta classification used local complications and organ failure to classify severity of acute pancreatitis. Multiple modifications have taken place throughout the years but the classification remained lacking in the assessment of the degree of organ failure. This has been addressed in the 2012 revised Atlanta classification, which identified 2 types of organ failure: transient organ failure that resolves within 48 hours and persistent organ failure lasting more than 48 hours. Three degrees of severity have been set as defined earlier.

In comparison with transient organ failure, persistent organ failure is significantly associated with the development of infected pancreatic necrosis and mortality. It also correlates positively with the need for percutaneous or surgical intervention.[24]

Sepsis can develop in the second stage of acute pancreatitis leading to multiorgan system failure with an associated increase in mortality.[2] Infection can be acquired through bacterial translocation of intestinal bacteria, which can be explained by the state of hypoperfusion associated with severe pancreatitis. Hospital-acquired infections can take place as well later in the second stage and are more prominent in mechanically ventilated patients or in those requiring invasive monitoring lines in the critical care setting. Moreover, it is also believed that patients with acute pancreatitis have a state of relative immunosuppression. Sepsis can be of either pancreatic or extrapancreatic source (blood, pulmonary, urinary, etc). The presence of pancreatic and extrapancreatic sepsis or extrapancreatic sepsis alone was found to have an increased risk of mortality when compared with pancreatic sepsis alone.[2] A reason for this finding is that pancreatic infection alone can be treated well with percutaneous drain placement. By contrast, extrapancreatic causes of infection are more insidious; ventilator-acquired pneumonia, for example, can be treated with antibiotics only and does not allow the option of drainage of the source. Surgical drainage of infected pancreatic necrosis should not be the first intervention if possible. It is well documented that early surgical intervention is associated with a dismal outcome.[25] On the contrary, when surgical intervention is needed, those with pancreatic infection actually fare better than those with sterile necrosis. It should be emphasized that the notion of delaying operative intervention should not interfere with prompt intervention for infected pancreatic necrosis. Most of these interventions can be accomplished through a percutaneous approach. The revised 2012 Atlanta classification defined infected necrosis through the presence of 1 of the 3 criteria: clinical with ongoing sepsis and radiologic manifestation of air on CT scan, documented positive culture on FNA, or secondary to instrumentation. Although some studies reported 67%-98% accuracy of FNA in detecting pancreatic infection, the practice of using FNA has been declining. The introduction of a percutaneous approach and the increasing practice of delayed operative intervention may have played into this observation. The indications for using FNA are not well defined, and its use is left up to the discretion of the managing clinician. It should also be noted that FNA has a false-negative value of approximately 25%.[26] Although infrequent, FNA carries the risk of bleeding and most importantly contamination of previously sterile necrosis, which is associated with increased morbidity and mortality.[21] Factors such as pancreatic necrosis, leukocytosis, elevated C-reactive protein (CRP) level, and fever were identified as risk factors for developing pancreatic infection.[27] Fungal infection is also known to carry a higher mortality rate than bacterial pancreatic infection.[2]

The need to adequately assess the severity of pancreatitis and predict its course has led to the development of multiple scoring systems. Some scoring systems adopted morphologic features of the gland whereas others used clinical and laboratory parameters to accomplish the task. Recently, single parameters have been studied with variable success. An ideal scoring system should be accurate, able to be used early on in the disease process, and be appropriate for reassessing the severity of the pancreatitis attack. The commonly used scoring systems based on their targeted benchmarks are summarized later. The common theme with scoring systems is the attempt to help identify the patient who is at high risk for major organ failure and death.

### *Radiologic scoring systems*

#### *Balthazar scoring system*

The Balthazar scoring system was developed in 1985 and assesses morphologic features of the gland on the nonenhanced contrasted CT.[28] This system had reasonable success and correlated well with severity and mortality. Its major limitation was the use of nonenhanced CT, which precluded assessment of pancreatic necrosis.

#### *CT severity index*

To get a better idea of necrosis, enhanced CT was introduced and the degree of pancreatic necrosis was categorized into 3 classes: less than 30%, 30%-50%, and greater than 50%. This system again focused on the gland itself and had better prediction of local complications but did not correlate well with clinically based scoring systems.[29]

#### *Modified CT severity index*

The recognition of imaging findings outside the pancreas per se led to the modified CT severity index. The addition of extrapancreatic complications in 2004 proved again to be accurate in predicting local complications and the need for future intervention[30] (Table 1).

### *Clinically based scoring systems*

#### *Ranson's criteria*

Ranson's criteria were developed by Ranson in 1970 and included 11 clinical and laboratory values (Table 2). Two sets of variables were required to fully assess severity of pancreatitis. The first set of variables includes 5 values and is taken on admission whereas the next 6 values on the second set are obtained 48 hours later. The main aim of the Ranson's criteria was to predict the risk of mortality in patients developing acute pancreatitis. Unfortunately, most studies have found the Ranson's score to have a sensitivity and a positive predictive value of less than 80%.[29] This scoring system was also found to be less accurate in predicting the severity of pancreatitis related to a biliary process.[31] Several modifications have been proposed throughout the years

**Table 1**
Modified CT severity index

| Criteria | Score |
|---|---|
| Pancreatic inflammation | |
| Normal pancreas | 0 |
| Intrinsic abnormalities with or without inflammatory changes in peripancreatic fat | 2 |
| Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis | 4 |
| Pancreatic necrosis | |
| None | 0 |
| $\leq 30\%$ | 2 |
| $> 30\%$ | 4 |
| Extrapancreatic complications | 2 |

**Table 2**
Ranson's criteria

| |
|---|
| On admission |
| WBC > 16,000 |
| Age > 55 y |
| Glucose > 200 mg/dL |
| AST > 250 U/L |
| LDH > 350 U/L |
| 48 h into admission |
| Hct decrease > 10% |
| BUN increase > 5 mg/dL |
| Ca < 8 mg/dL |
| Arterial $pO_2$ < 60 mm Hg |
| Base deficit > 4 mg/dL |
| Sequestration of fluids > 6 |

The predicted mortality: score < 3 = 1%, 3-4 = 15%, 5-6 = 40%, and > 6 = 100%. AST, aspartate aminotransferase; Ca, calcium; Hct, hematocrit; LDH, lactate dehydrogenase; WBC, white blood cell.

but with no significant improvement in predicting complications and mortality.[32] One of the limitation of Ranson's criteria is that the score did not address patient-specific comorbidities. It is interesting that Ranson's criteria focused on the importance of the early time frame in acute pancreatitis, as this has been the focus of many predictive models for acuity. In addition, the Ranson's criteria does in fact measure organ failure through many of its values, for example, lung function is reflected by $O_2$ and renal function is reflected in the blood urea nitrogen (BUN). This was very forward thinking at the time and has illustrated the common theme of organ dysfunction that is the cornerstone of SAP.

Although the recognition of the importance of the first 48 hours is important with the Ranson's criteria, the drawback is the lack of a complete set of data until the 48-hour time point. This effectively means that any predictive models cannot accurately predict mortality until 48 hours into the process; the ideal predictive model should invoke variables at admission to predict morbidity and mortality.

*Imrie or Glasgow score*

Imrie or Glasgow scoring systems included age on admission and 8 other physical and laboratory parameters obtained in the first 48 hours after admission (Table 3). Many modifications have been applied and although slight improvements in assessing gallstone-related pancreatitis have been achieved, its sensitivity remained less than 80% with positive predictive value less than 70%.[29] Like Ranson's criteria, the 48-hour delay is one of the limitations of this scoring system.

**Table 3**
Imrie Glasgow criteria

| | |
|---|---|
| P | $PaO_2$ < 60 mm Hg |
| A | Age > 55 y |
| N | Neutrophils (WBC) > 15,000 |
| C | Calcium < 2 mmol/L |
| R | Renal function: urea > 16 mmol/L |
| E | Enzymes LDH > 600 U/L |
| A | Albumin < 32 g/L |
| S | Sugar (blood glucose > 10 mmol/L |

The predicted mortality: score 0-2 = 2%, 3-4 = 15%, 5-6 = 40%, and 7-8 = 100%. LDH, lactate dehydrogenase; WBC, white blood cell.

*Acute Physiology and Chronic Health Evaluation II score*

In total, 35 clinical criteria were used in the acute physiology and chronic health evaluation (APACHE) scoring system and reduced to 11 variables in APACHE II. A score greater than 10 on admission was found to have a sensitivity and a specificity of 71% and 91%, respectively, for predicting the severity of acute pancreatitis. At 48 hours, a score greater than 9 has 75% sensitivity and 92% specificity in predicting the severity of acute pancreatitis.[31] In addition to its flexibility, APACHE II allows recalculation and reassessment during the course of the disease. Moreover, APACHE II at 24 hours performed better at predicting mortality than Ranson's criteria or Imrie score at 48 hours.[33]

The main advantage to the APACHE II scoring system is that this is a universally recognized system for critically ill patients and is used across all disease processes. The inclusion of many patient-specific variables is helpful. The APACHE II score on admission can be used to predict the severity of disease.

*Organ failure related scoring systems*

The correlation between organ failure and morbidity and mortality is well documented. Theoretically, the use of scoring systems that evaluates the presence and degree of organ failure should have the ability to predict morbidity and mortality. Although this seems an intuitively correct idea, these scoring systems have been applied, but are yet to be validated in large studies.

*MOC or Goris*

The Goris multiorgan failure score assesses 7 major organs' dysfunction and predicts survival based on the presence or absence of organ failure. This system has some success at monitoring organ dysfunction but this scoring system has not translated into mortality prediction.

*Marshall score*

The degree of organ failure is included in the Marshall score. To further eliminate confounding laboratory criteria seen in gallstone-related pancreatitis, hepatic dysfunction was excluded (Table 4). In a study, the Marshall score was found to be comparable to APACHE II in predicting mortality.[29]

*Sequential organ failure assessment*

The sequential organ failure assessment (SOFA) system is another system that adopted quantification of organ failure in its scoring (Table 5). A score greater than 4 at 48 hours has 86% sensitivity and 79% specificity in predicting mortality.[33] In the intensive care unit (ICU) population, a score greater than 8 correlated with mortality.[29] SOFA was also found to be comparable to the Marshall score in predicting in-hospital mortality. Cardiovascular, renal, and hepatic failure were found to be independently associated with in-hospital mortality.

**Table 4**
Modified Marshall scoring system

| Modified Marshal | Score | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Organ system | | | | | |
| CVS | SBP > 90 | SBP < 90, responsive to fluid | SBP < 90 | SBP < 90, pH < 7.3 | SBP < 90, pH < 7.2 |
| Respiratory P/F ratio | > 400 | 301-400 | 201-300 | 101-200 | < 101 |
| Renal creatinine, mg/dL | < 1.4 | 1.4-1.8 | 1.9-3.6 | 3.6-4.9 | > 4.9 |

Organ failure is defined by the presence of score ≥ 2.
CVS, cardiovascular system; P/F ratio, $pO_2/FiO_2$ ratio; SBP, systolic blood pressure.

**Table 5**
Sequential organ failure assessment (SOFA) scoring system

| SOFA | Score | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Organ system | | | | | |
| CVS | MAP > 70 | MAP < 70 | Dopa < 5 or Dobu | Dopa > 5 or Epi ≤ 0.1 or Norepi = < 0.1 | Dopa > 15 or Epi > 0.1 or Norepi > 0.1 |
| Respiratory P/F ratio | > 400 | < 400 | < 300 | < 200 and on ventilation | < 100 and on ventilation |
| Renal creatinine | < 1.2 | 1.2-1.9 | 2.0-3.4 | 3.5-4.9 | > 5 |
| Hepatic bilirubin | < 1.2 | 1.2-1.9 | 2.0-5.9 | 6.0-11.9 | > 12 |
| Hematology platelets | > 150 | < 150 | < 100 | < 50 | < 20 |

CVS, cardiovascular system; Dobu, dobutamine, μg/kg/min; Dopa, dopamine, μg/kg/min; Epi, epinephrine, μg/kg/min; MAP, mean arterial blood pressure, mm Hg; Norepi: norepinephrine, μg/kg/min; P/F ratio: $pO_2/FiO_2$ ratio.

An advantage of this scoring system is its ease of use; however, this scoring system still needs to be validated in large studies.

*Single parameter scoring systems*

The scoring systems listed earlier have focused on multiple variables. Single variables have also been used to predict outcome in patients with acute pancreatitis.

*Hematocrit*

An elevated hematocrit level is a surrogate of fluid sequestration and hypoperfusion. A hematocrit level greater than 44% on admission correlates with the development of organ failure and pancreatic necrosis. A level greater than 50% was found to correlate with SAP. Levels between 41% and 44% did not predict either severity or mortality.[34] A change of the hematocrit level was studied as well, but no prediction value was identified.[29] Interestingly, the duration of abdominal pain before admission was found to affect severity only when associated with higher hematocrit values.[35] Similarly, the hematocrit is a valuable prognostic indicator when applied in the transferred patient population. In that sense, the hematocrit is a proxy to the adequacy of the resuscitation effort.

*Creatinine or BUN*

The serum creatinine level and BUN are surrogate of intravascular hypovolemia and renal function. A creatinine level greater than 1.8 mg/dL was found to be associated with the development of pancreatic necrosis.[36] Nevertheless, neither creatinine nor BUN has been documented as a reliable solo predicting parameter.[29]

*C-reactive protein*

Multiple studies have evaluated the role of CRP in acute pancreatitis. A cutoff level of 150 ng/L within 48 hours was found to be 70%-80% accurate in differentiating mild from SAP.[27] The CRP is also known to peak 72-96 hours later in the disease process, and a level equal or greater than 200 ng/L after 48 hours has even better predictive value of a worse outcome.[29] CRP is considered the parameter of choice in differentiating necrotizing from interstitial pancreatitis. The CRP is of no value in predicting the development of infection, organ failure, or mortality in the early phase of the acute attack.

*Procalcitonin*

The use of procalcitonin as a surrogate for infection has been increasingly applied in critical care clinical practice. Its use as a predictor for the development of infected necrosis has been promising as well. A cutoff level of 1.8 ng/mL in the first few days was found to be 90% sensitive and specific in predicting infected necrosis. A level greater than 0.4 ng/mL in the first 24 hours from the onset of symptoms is 97% sensitive and 73% specific in predicting organ failure. In 48-96 hours from symptom onset, a level greater than 3.8 ng/mL can predict infected pancreatic necrosis and mortality with a sensitivity and a specificity of 79% and 93%, respectively.[29] Procalcitonin may be the best single indicator of morbidity and mortality with acute pancreatitis. Further studies to evaluate the use of procalcitonin levels are required.

## Radiologic diagnosis

Radiologic imaging has become increasingly important in staging and treating patients with acute pancreatitis.[37,38] The revision of the Atlanta classification focuses heavily on morphologic criteria for defining the various manifestations of acute pancreatitis as outlined principally by means of CT. This revision places a major emphasis on revised or new criteria for PFCs and revises some of the clinical criteria and terminology.[21]

According to the revised Atlanta classification, contrast-enhanced CT is the primary tool for assessing the imaging-based criteria because it is widely available for these acutely ill patients and has a high degree of accuracy.[39] Contrast-enhanced CT is especially suited for evaluating the extent of acute pancreatitis, helping to assess complications, and monitoring of treatment response through follow-up studies. Not all patients with acute pancreatitis need to undergo contrast-enhanced CT. Contrast-enhanced CT is not indicated initially in patients with acute pancreatitis who have no clinical signs of severe pancreatitis and who show rapid clinical improvement. However, contrast-enhanced CT should be performed in patients who develop, or are likely to develop, SAP or complications related to acute pancreatitis. The ideal time for assessing these complications with CT is after 72 hours from onset of symptoms. CT should be repeated when the clinical picture drastically changes, such as with sudden onset of fever, decrease in hematocrit level, or sepsis. CT also is useful to guide catheter placement for drainage and to assess success of treatment in patients who underwent percutaneous drainage or other interventions.[39,40]

Furthermore, in patients with a first episode of pancreatitis who are older than 40 years and have no identifiable cause for pancreatitis, contrast-enhanced CT should be used to exclude a possible neoplasm.[39] The radiologist should address whether pancreatic necrosis is present, characterize pancreatic parenchymal and extrapancreatic fluid collections, and describe the presence of ascites and extrapancreatic findings, such as gallstones, biliary dilatation, venous thrombosis, aneurysms, and contiguous inflammatory involvement of the gastrointestinal (GI) tract.[41]

We find that an initial CT scan can be very helpful in assessing whether a pancreatic cyst is a neoplasm, WOPN, or pancreatic pseudocyst. The initial CT scan in a new episode of pancreatitis should not show a well-formed cyst. If this is seen, there should be concern for a cystic neoplasm causing the episode of pancreatitis, rather than the cyst being a result of the pancreatitis. The authors have a low threshold to obtain CT scans in patients at presentation with their first episode of pancreatitis. Moreover, a CT scan should be obtained if there is any question of correct diagnosis of acute pancreatitis.

According to the revised Atlanta classification, magnetic resonance imaging (MRI), trans-abdominal US, or endoscopic US (EUS) may be used for special indications.[39] MRI is reserved for the detection of choledocholithiasis not visualized on contrast-enhanced CT images and to further characterize collections for the presence of nonliquefied material (solid necrotic debris).[42] Nonliquefied material refers to solid and semisolid components, usually pancreatic and extrapancreatic debris and necrotic fatty tissue, and may appear on contrast-enhanced CT images as a homogeneous or a heterogeneous fluid collection. MRI has an important role in

patients in whom contrast-enhanced CT is contraindicated (eg, owing to allergic reaction to iodinated intravenous contrast agents or pregnancy).[39] Transabdominal US can be helpful for determining the presence of stones in the gall bladder, but it is less accurate than contrast-enhanced CT or MRI for visualizing distal common bile duct stones and has the disadvantage of being operator dependent.[43] The presence of gas can obscure even a view of the gall bladder, let alone the distal bile duct. US is user dependent and very dependent on the body habitus of the patient.[44]

In patients with renal insufficiency who cannot undergo administration of iodinated contrast material or gadolinium, unenhanced CT or MRI may be used.[45] ERCP has no role in this morphologic imaging-based classification of acute pancreatitis, as magnetic resonance cholangiopancreatography (MRCP) should accurately delineate the ductal anatomy of the pancreas. The imaging-based revised classification involves careful assessment of CT images of collections of fluid or nonliquefied material in and around the pancreas or both (ie, areas of pancreatic parenchymal and peripancreatic necrosis). The terminology for fluid collections is completely revised. It is important for the radiologist to adopt this new nomenclature so that imaging descriptions are standardized, and communication with clinical and surgical colleagues is precise.[39]

### *Interstitial edematous pancreatitis*

In patients with interstitial edematous pancreatitis, contrast-enhanced CT demonstrates acute pancreatitis as localized or diffuse enlargement of the pancreas, with normal homogeneous enhancement or slightly heterogeneous enhancement of the pancreatic parenchyma related to edema. The peripancreatic and retroperitoneal tissue may appear normal, usually in early mild disease, or may show mild inflammatory changes in the peripancreatic soft tissue that appear as mild fat stranding with varying amounts of peripancreatic fluid. On a contrast-enhanced CT study obtained within the first several days of acute onset of pancreatitis, the pancreas occasionally demonstrates increased heterogeneous enhancement of the parenchyma that cannot be characterized definitively as either interstitial edematous pancreatitis or ill-defined necrosis. With these findings, the presence or the absence of pancreatic necrosis must be described initially as indeterminate. Contrast-enhanced CT performed 5-7 days later permits definitive characterization.[46]

The revised Atlanta classification system distinguishes 3 forms of acute necrotizing pancreatitis, depending on location: pancreatic parenchymal necrosis alone, peripancreatic necrosis alone, or pancreatic parenchymal necrosis with peripancreatic necrosis.

This categorization represents a distinct change from the initial classification. All 3 types can be sterile or infected.[39]

### *Necrotizing pancreatitis*

#### *Pancreatic parenchymal necrosis alone*

Pancreatic parenchymal necrosis alone is encountered in fewer than 5% of patients and appears on contrast-enhanced CT images as lack of parenchymal enhancement.[47] In the first week of necrotizing pancreatitis, the finding of the contrast-enhanced CT scan demonstrates necrosis as a more homogeneous nonenhancing area of variable attenuation and later in the course of the disease, as a more heterogeneous area. The radiologic changes are the result of a process in which the nonviable and necrotic tissues (primarily pancreatic parenchyma and peripancreatic fat) slowly begin to liquefy. Often the extent of parenchymal necrosis is divided on contrast-enhanced CT studies into 3 categories: less than 30%, 30%-50%, or greater than 50% of the gland involved.[48] In a newer modified CT grading system, only 2 categories are distinguished: less than 30% and greater than 30%.[30] At times, areas of no or poor enhancement that are estimated to be less than 30% in the early phase may actually be findings of edema

rather than necrosis.[30] A definitive diagnosis in these patients requires a follow-up study. This is best performed at least 5 days after the start of the episode of pancreatitis.

*Peripancreatic necrosis alone*

Peripancreatic necrosis alone is encountered in approximately 20% of patients and can be difficult to confirm.[47] Its presence is diagnosed when heterogeneous areas of nonenhancement are visualized that contain nonliquefied components. Peripancreatic necrosis is commonly located in the retroperitoneum and lesser sac. The clinical importance of peripancreatic necrosis alone lies in the fact that patients with this condition have a better prognosis than do patients with pancreatic parenchymal necrosis.[49] Nevertheless, patients with peripancreatic necrosis have a higher morbidity rate than do patients with interstitial edematous pancreatitis only.[50]

*Pancreatic parenchymal necrosis with peripancreatic necrosis*

Acute pancreatic parenchymal necrosis with peripancreatic necrosis is the most common type and is encountered in 75%-80% of patients with acute necrotizing pancreatitis.[47] The radiologic appearance of pancreatic parenchymal necrosis with peripancreatic necrosis is a combination of the findings described earlier for pancreatic parenchymal necrosis alone and peripancreatic necrosis alone. Peripancreatic necrosis associated with full-width necrosis of the pancreatic parenchyma may be connected to the main pancreatic duct.[51]

*Pancreatic and peripancreatic collections*

In the revised Atlanta classification, an important distinction is made between fluid and nonliquefied collections.[39] The acute collections are referred to as either acute peripancreatic fluid collection or as acute necrotic collection, depending on the absence or the presence, respectively, of necrosis. Interstitial edematous pancreatitis can be associated with acute peripancreatic fluid collection and, over time, with pancreatic pseudocysts. Necrotizing pancreatitis in its 3 forms can be associated with acute necrotic collection and, over time, with WOPN. All of these collections can be sterile or infected.[39] The imaging characteristics of each of these fluid collections are outlined later.

*Acute peripancreatic fluid collection*

Peripancreatic fluid collections without nonliquefied components arising in patients with interstitial edematous pancreatitis during the first 4 weeks are referred to as acute peripancreatic collections. These collections have a density of 0-30 HU on CT. They are caused by pancreatic and peripancreatic inflammation or by rupture of one or more small peripheral pancreatic side duct branches. Acute peripancreatic fluid collections conform to the anatomical boundaries of the retroperitoneum (especially the anterior pararenal fascia), are usually seen immediately next to the pancreas, and have no discernable wall. Fluid collections in the pancreatic parenchyma should be diagnosed as necrosis and not as acute peripancreatic fluid collections.[39] These acute peripancreatic fluid collections are not rounded and do not display mass effect.

In the first week of acute pancreatitis, a distinction between acute peripancreatic fluid collection and acute necrotic collection may be difficult or impossible, because both collections may appear as areas of nonenhancement. If nonenhancing areas of variable attenuation are seen in these collections, the diagnosis of peripancreatic necrosis with nonliquefied components is suggested. Nonliquefied components are primarily hemorrhage, fat, and necrotic fat. Such findings are not compatible with interstitial edematous pancreatitis, and, in these cases, the process should be diagnosed as acute necrotizing pancreatitis with peripancreatic necrosis alone. A diagnosis of peripancreatic necrosis based on contrast-enhanced CT findings often cannot be made specifically but can be suspected when slightly heterogeneous peripancreatic collections are seen. After 1 week from onset, the collection usually becomes clearly heterogeneous, and necrosis can be diagnosed on contrast-enhanced CT images.[41]

*Pseudocyst*

Within 4 weeks from the onset of acute interstitial edematous pancreatitis, an acute peripancreatic fluid collection may gradually transition into a pseudocyst. On contrast-enhanced CT images, pseudocysts can be diagnosed as well-circumscribed thin-walled, usually round or oval peripancreatic fluid collections of homogeneously low attenuation that are surrounded by a well-defined enhancing wall (capsule consisting of fibrous or granulation tissue) with a density less than 20 HU. On MRI, pseudocysts appear hypotense on T1-weighted and hyperintense on T2-weighted images.[42] Stagnant fluid appears bright on T2-weighted imaging, making the delineation of necrotic material and fluid better seen on MR images.[52] In the rare event in which an acute peripancreatic fluid collection develops an enhancing capsule earlier than 4 weeks after the onset of acute interstitial edematous pancreatitis, it should be characterized as a pseudocyst.[39] The pseudocyst contains fluid with increased amylase and lipase activity owing to communication with the pancreatic ductal system. However, many pseudocysts seal off such a communication and vanish spontaneously. Demonstrating the presence or the absence of communication with the pancreatic duct may be important as it may help determine the management. Persistent communication with the pancreatic duct can be shown on contrast-enhanced CT images and curved planar reconstructions, but MRCP is usually more accurate[53] (Fig 8). In the rare case in which a pseudocyst becomes infected, it contains purulent liquid but no nonliquefied material. An infected pseudocyst is diagnosed on CT images by the presence of gas within the pseudocyst or, in the absence of gas, by means of FNA with gram staining and culture for bacteria or fungal organisms.[49]

In rare instances, a pseudocyst can develop in patients after pancreatic resection owing to necrosis and subsequent leakage of pancreatic secretions from the remaining duct or in patients with disconnected duct syndrome[51] (Fig 9). Again, imaging should show the lack of necrotic material within a pseudocyst; a pure pseudocyst is a rare entity.

*Acute necrotic collections*

In the first 4 weeks after development of necrotizing pancreatitis, a persistent collection is to be diagnosed as an acute necrotic collection that contains both fluid and necrotic material of various amounts (some of which are loculated) and is to be distinguished from acute peripancreatic fluid collection.[39] The revised Atlanta classification carefully avoids the term fluid collection for this stage to emphasize the fact that these collections contain more than fluid. In these acute necrotic collections, liquefaction of the necrotic tissue occurs gradually (usually within 2-6 weeks).[39] More and more liquefaction develops as the necrotic tissue breaks down. Within the first week, both acute peripancreatic fluid collections and acute necrotic collections can manifest as homogeneous nonenhancing areas. Usually, the distinction on contrast-enhanced CT images should become possible after the first week, because these collections with necrotic debris appear more complex on images.[39] An acute necrotic collection may or may not have a connection to the disrupted pancreatic ductal system within the necrosis.

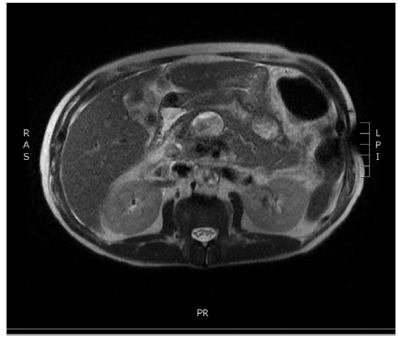


**Fig. 8.** MR image shows communication between pancreatic duct and pancreatic fluid collection.

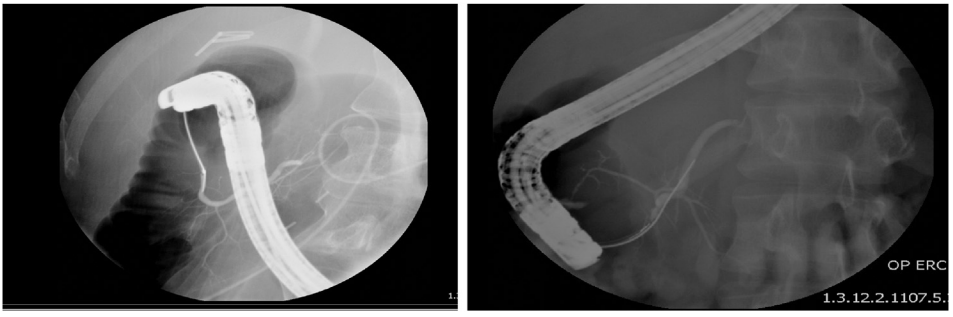


**Fig. 9.** Disconnected pancreatic duct evident on ERCP.

*Walled-off pancreatic necrosis*

Over time (usually at or after 4 weeks), the acute necrotic collection matures and develops a thickened nonepithelialized wall between the necrosis and the adjacent tissue.[39] This maturing collection is called a WOPN. Previous terms used for this phenomenon include pancreatic sequestration, necroma, and organized pancreatic necrosis and are a manifestation of the late stage of an acute necrotic collection. WOPN was not recognized in the original Atlanta classification.[39] Like acute necrotic collection, WOPN may involve the pancreatic parenchymal tissue and the peripancreatic tissue, the peripancreatic tissue alone, or the pancreas alone. Any apparent fluid collection that occupies or replaces portions of the pancreatic parenchyma should be called a WOPN after 4 weeks from the onset of necrotizing pancreatitis. This WOPN may or may not be infected. Demonstrating a communication of the WOPN with the pancreatic duct is not necessary for the Atlanta classification, but it may change the management. In contrast to a pseudocyst, WOPN contains necrotic pancreatic parenchyma or necrotic fat.[39] Solid components in these collections are identified better on US and T2-weighted MRIs than on CT[54] (Fig 10). A pancreas protocol MRI study should include a fat-suppressed contrast-enhanced dynamic T1-weighted gradient-echo sequence.[55] Enlargement of the pancreatic and parenchymal edema and fat stranding are well evaluated on T1-weighted images. The sensitivity of MRI for detection of solid debris has been shown to be 100% compared with 25% for that of CT.[55]

EUS is a minimally invasive test that provides high-resolution imaging of the pancreas. EUS involves passage of a specialized scope through the esophagus, stomach, and duodenum. Transabdominal US is often used for the evaluation, patients with acute pancreatitis to rule out gall bladder stones, sludge, and biliary dilation. Unfortunately, it does a poor job of imaging the distal common bile duct where stones might reside. EUS provides a high-quality view of the bile duct from the ampulla of Vater to the hepatic hilum. EUS can also decrease the number of unnecessary ERCP procedures in patients with suspected biliary pancreatitis. Tumors and other causes of bile duct obstruction can also cause acute pancreatitis and may be difficult to detect on cross-sectional imaging. EUS, on the contrary, can detect small pancreatic masses less than 2 cm, which can be missed on CT scans. Also, structural abnormalities of the pancreas like pancreatic divisum can be seen with EUS.[57]

Pancreatitis is associated with a wide variety of complications affecting the gland and the surrounding structures. Contrast-enhanced CT is the primary imaging modality for initially identifying local complications. MRI and US examinations can be useful to evaluate the content of fluid collections. The use of a new standard terminology is important to facilitate communication between radiologist, gastroenterologist, and surgeon.

In summary, imaging should distinguish acute pancreatitis based on the presence or the absence of necrosis, location of findings (pancreatic or extrapancreatic), and the presence or the absence of infection, as illustrated by air in the collection. The older nomenclature of pancreatic pseudocyst has fallen out of favor and most collections will be termed WOPN. The use of correct and understandable terminology can allow for correct communication between different services.[57]

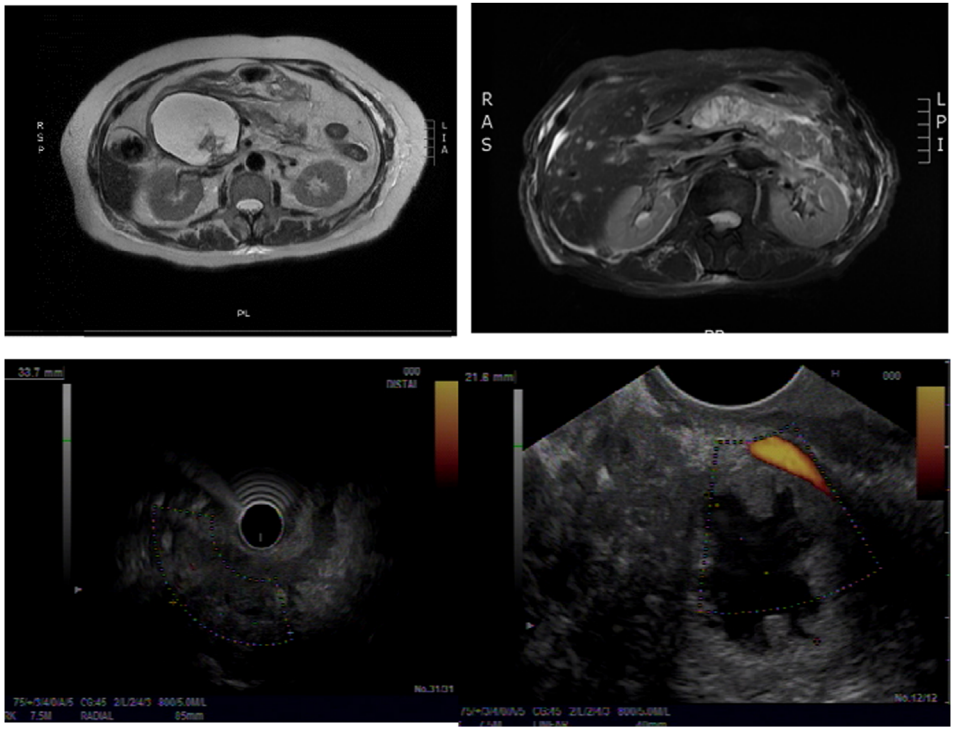


**Fig. 10.** Nerotic soild component of WOPN on MR image (upper panels) and EUS (lower panels). (Color version of figure is available online.)

## Management

Patients with acute pancreatitis present to the hospital with abdominal pain. The first step in management is ensuring that the diagnosis of acute pancreatitis is in fact correct. Acute pancreatitis is diagnosed based on clinical, laboratory, and imaging criteria as discussed earlier. A history of an antecedent alcoholic binge may be obtained on history in those patients that have alcohol-induced pancreatitis.

The original criteria proposed by Ranson required the assessment of several variables at admission: alanine aminotransferase level, lactate dehydrogenase level, serum glucose level, white cell count, and age. Other scoring systems for acute pancreatitis have been developed and modified with variable success.

Multiple classification systems have been instituted to assess the degree of severity of the acute attack and to create a common language when dealing with local complications of pancreatitis. The Atlanta criteria were the most popular system that was developed in the modern era.[47] The Atlanta criteria were modified in 2012.[21] These modified criteria ask for only 2 of 3 indicators to make the diagnosis: (1) abdominal pain consistent with pancreatitis, (2) elevated lipase or amylase level to at least 3 times normal, and (3) cross-sectional imaging confirming pancreatic inflammation.

A key point is that the diagnosis of acute pancreatitis can now be made on clinical and laboratory studies only rather than imaging at presentation. This has been a change in paradigm in the diagnosis of acute pancreatitis.

The authors would like to point out that imaging is in fact critical if there is any question about the diagnosis. For example, if there is a possibility of perforated viscous at presentation, a dedicated CT scan is of utmost importance.[58] Similarly, if the differential diagnosis includes

bowel obstruction in the patient who is vomiting and who has had several operations previously, cross-sectional imaging might change the treatment plan completely. Therefore, it is the authors' preference to obtain cross-sectional imaging at presentation if there is any concern regarding the diagnosis of acute pancreatitis. Imaging in acute pancreatitis may in fact show very subtle findings of peripancreatic edema only in the early phase of the disease.

Once acute pancreatitis has been diagnosed, the treatment proceeds along the pathways outlined later. The treatment plan will vary depending on the timing after the onset of acute pancreatitis.

### *Acute phase—First 48 hours and first week*

This is the phase of injury that occurs in the first 48 hours after presentation with acute pancreatitis.[18] The original Ranson's criteria were used to evaluate the severity of acute pancreatitis at presentation partly to assess the need for a higher level of care.[31] It was the author's preference to place those patients with 3 or more Ranson's criteria at presentation in the ICU with urinary catheter placement and aggressive fluid resuscitation. Currently, the concept of SIRS response has been used to assess the severity of pancreatitis.[24] The diagnosis of SIRS is made when 2 or more of the following criteria are present: (1) heart rate elevation $>90$ beats per minute, (2) temperature $<36^{\circ}$C or $>38^{\circ}$C, (3) white blood cells $<4000$ or $>12{,}000/\text{mm}^3$, and (4) respiratory rate $>20$ per minute.

Another scoring system that has assessed the severity of acute pancreatitis at presentation is the bedside index for severity of acute pancreatitis score,[59] which includes the following parameters: (1) BUN $>$ 25 mg/dL, (2) mental status changes (Glasgow coma score $<15$), (3) evidence of SIRS, (4) age $>60$ years, and (5) pleural effusion on imaging study.

This scoring system has been used to predict in-hospital mortality after an episode of acute pancreatitis. Whichever scoring system is being used, the patient that appears to be ill and deteriorating is the patient that is going to develop pancreatic necrosis. These are the patients that need urgent and intensive intervention. Another indicator that has been associated with an increased risk of pancreatic necrosis has been the level of serum creatinine. A rise in the serum creatinine level to more than 1.8 mg/dL in the first 48 hours after admission is associated with a 93% positive predictive value of pancreatic necrosis.[60] This is of course the group of patients that will need aggressive interventions. Another measure of renal function, BUN, has also been linked to a high risk of deterioration: a BUN greater than 20 mg/L at presentation is associated with an increased risk of deterioration.[36] A rise of more than 5 mg/dL in the first 48 hours after the diagnosis of acute pancreatitis is associated with an increase in infected pancreatic necrosis.[36] In this latter study, the authors looked retrospectively at 281 patients presenting with acute pancreatitis to the Mayo Clinic hospitals. They found that on univariate analysis, SIRS $\geq$ 2 on admission, a rise in BUN $>$ 5 mg/dL within 48 hours of presentation, persistent SIRS, or development of organ failure within 48 hours was associated with the development of infected pancreatic necrosis. A rise in BUN $>$ 5 mg/dL was the only factor that remained significant on multivariate analysis. The reader can infer that renal function is a good surrogate for the injury that is ongoing in the retroperitoneum. A mild injury results in minimal fluid shifts, whereas a severe “burn” to the retroperitoneum results in fluid shifts, hemoconcentration, compromised renal function, etc. The issue of which patient is going to develop necrosis and whether necrosis is linked to inadequate resuscitation is an interesting one. This is an area that is ripe for research. However, based on current criteria, a SIRS response at presentation with renal dysfunction should indicate a high likelihood of pancreatic necrosis. This should tip the clinician off to the need for higher level of care and the need a for aggressive fluid resuscitation.

#### *Fluid management*

The use of aggressive fluid resuscitation is the mainstay of treatment of acute pancreatitis in the initial phase. There have been data to support the use of lactated ringers rather than normal saline in the early phase of resuscitation.[1] There has also been a review that suggested that

crystalloid or colloid were equally effective in treating patients with acute pancreatitis.[61] There was also a study that looked at supplementing normal saline with hetastarch and glutamine.[62] Patients with SAP were randomized to receive normal saline, normal saline and hetastarch (SH), or SH and glutamine. The authors found that the SH and glutamine group had improved outcomes in terms of renal dysfunction, adult respiratory distress syndrome, abdominal infection, and measured serum proinflammatory cytokines. Unfortunately, this resuscitation fluid has not been readily available. It is the author's practice to use lactated ringer's solution in the initial phase of treatment. Studies comparing aggressive resuscitation in the early phase with delayed resuscitation showed an improvement in the SIRS response of these patients.[63] The goal of fluid resuscitation in the early phase is similar to the management of the burn patients: urine output is the main measure of adequate resuscitation. Placement of a urinary catheter in patients that display worrisome characteristics based on the scoring systems described earlier is usually performed to measure the urine output accurately.

Many treating physicians are cautious in their resuscitation because the patient with acute pancreatitis may have effusions on imaging studies. There is great concern about placing these patients into volume overload which may lead to intubation. In fact, fluid replacement is the key element to success in treating patients with acute pancreatitis. Early and aggressive resuscitation has been shown to improve the SIRS response in these patients.[63] Measures of response to fluids include a decrease in heart rate, increase in blood pressure, increase in urine output, and a decrease in the hemoconcentration that is often seen in these patients at presentation. Resuscitation in the first 48 hours is the mainstay of therapy of the patient with pancreatitis. However, many of these patients with SAP present to hospitals where the clinician may be cautious with fluid resuscitation, especially in a patient that is displaying tachypnea and tachycardia. A useful intervention in the patient with severe pancreatitis would be to transfer these ill patients to a center that deals with severe pancreatitis patients on a frequent basis.

*Use of antibiotics*

The role of antibiotics has been of great debate over the decades.[64] Those who have advocated antibiotic use have argued that they would penetrate the gland and decrease the likelihood of superinfection in the necrotic gland. Those that have argued against antibiotics have suggested that the organ might get infected later and saving antibiotics for that time would aid in preventing resistant organisms. There have been several studies in the last decade that have attempted to answer this question. Earlier studies were smaller and less well controlled but suggested no improvement in outcomes with the use of antibiotics.[64] Early data with smaller patient cohorts suggested an improvement in infection rates with the use of prophylactic antibiotics.[64] There were then several meta-analyses of smaller studies that suggested that antibiotics did not in fact have any effect on outcomes.[65] There have now been 3 well-designed prospective randomized studies that have looked at the role of prophylactic antibiotics. These studies have been conducted across continents and have shown similar results: no improvement in rates of infected pancreatic necrosis and mortality with early antibiotic use.[66] A circumstance that is different is the patient with acute cholangitis. These patients need antibiotics to cover a biliary source (rather than the antibiotics that are targeted for concentration in the pancreas—carbapenems in general). The development of infected pancreatic necrosis does not occur in the early phase. The studied goal of early, prophylactic antibiotic use was to look at the end point of infected necrosis. As such, it is clear now that antibiotics are not recommended in the early phase of acute pancreatitis in the absence of cholangitis.

*Role of early ERCP*

There are 2 potential scenarios where ERCP may have a theoretical role. The first is biliary pancreatitis in the patient who has passed a stone already as noted by decrease in liver function tests. The theoretical benefit in this patient would be to perform a sphincterotomy and increase drainage of the pancreas with or without a pancreatic ductal stent. The second scenario is

cholangitis to relieve the obstruction to the bile duct that is leading to potential cholangitis in the patients with acute pancreatitis.

The American College of Gastroenterology has issued a guideline statement regarding the management of acute pancreatitis.[67] This group has recommended urgent ERCP within 12-24 hours if the patient has clinical signs of cholangitis.[68] The use of pancreatic stents and rectal nonsteroidal anti-inflammatory drugs (only if there is no renal dysfunction) is recommended to lower the risk of pancreatitis after ERCP and not, per se, to improve the ongoing episode of biliary pancreatitis. There has been a meta-analysis of 7 studies looking at the role of early ERCP in patients with acute pancreatitis that found no improvement in morbidity or mortality.[16] However, these studies had small numbers of patients with SAP and as such the studies were not well powered for detection of a benefit of ERCP. An ongoing well-designed Dutch study looking at the role of early ERCP is underway in patients with SAP owing to a biliary source (Anesthesia Preoperative Evaluation Clinic trial). The data from this study will be very helpful in determining the role of early ERCP in patients with biliary pancreatitis. At this time, the use of early ERCP is reserved for those patients who present with cholangitis and is not currently recommended as a tool to decrease the severity of acute pancreatitis itself.

*Role of octreotide*

Octreotide is an agent that blocks pancreatic secretion through blockage of the somatostatin receptor.[69] There have been 2 studies looking at the role of octreotide in preventing the progression of patients to SAP. In a study, 236 patients with predicted severe attack were randomized to control, low-dose octreotide (low-O-25 μg/h × 7 days), or high-dose octreotide groups (high-O-50 μg/h × 3 days + 25 μg/h × 4 days).[70] The authors found no difference in progression to SAP between the low-dose and control groups. However, the high-O group compared with the low-O group resulted in fewer patients progressing to SAP (37.5% vs 59.8%, respectively). The mechanism is thought to be via blockade of somatostatin receptor and a rise in serum somatostatin level. Another study examined the role of octreotide in reducing progression to SAP and development of complications in patients with obesity.[71] The authors randomized patients with obesity to standard therapy vs standard therapy with octreotide (50 μg/h × 3 days). The study found that the latter group developed fewer local complications (4.9%) compared with the control group (19%). A problem with this study was that the definition of obese in this study was a body mass index $>25$, which may not fall into more generally accepted definition obesity.

These data together raise the question of whether octreotide might have a role in the early treatment of the patient with acute pancreatitis. At this time, there is no defined role for octreotide in the management of the patient with acute pancreatitis.

*Nutrition*

Nutrition in the patient with acute pancreatitis is important. Many theories have evolved over feeding. A theory is that “resting” the pancreas by not using the GI tract may have benefit to resolution of acute pancreatitis.[72] Other theories have revolved around the maintenance of the gut barrier, which can reduce gut permeability if the GI tract is used for nutrition.[73] Infections related to lines needed for total parenteral nutrition (TPN) have also played a role in the current thinking about nutrition in acute pancreatitis. In the current era, the main area of interest has been the comparison of parenteral nutrition (PN) to enteral nutrition (EN), and the comparison of EN through an oral route vs through a tube of some type.[74] Most studies have demonstrated a benefit to EN over PN. A meta-analysis examined all reports that focused on initiation of EN vs PN in the first 48 hours after admission.[75] The authors identified 11 reports that met their criteria, of which 2 were retrospective in nature. They examined early EN compared with late EN or TPN, which was an interesting aspect to this reports. The authors were attempting to look not just at the route of nutrition but also the timing of nutrition. The article found that early EN was beneficial in all domains examined: infectious complications as a whole after acute pancreatitis, catheter-related infections, hyperglycemia, pancreas-specific infection, organ failure, length of

hospital stay, and mortality. Interestingly, pulmonary complications were not significantly different between the 2 groups. These data have led to the recommendation that patients with acute pancreatitis receive enteral feeding early. It should also be stressed that the enteral route should be used with caution in patients requiring vasopressor support in the early phase of pancreatitis owing to the fear of relative intestinal ischemia.

The next issue is whether gastric feeding or nasojejunal feeding is superior in patients with SAP. A prospective, randomized study examined this question. In total, 78 patients with SAP were randomized to gastric or jejunal feeding.[74] The authors found that there was a decrease in infectious complications in the nasogastric compared with the nasojejunal route. However, the study was not designed to answer this question and so the conclusion was that gastric feeding was not inferior to jejunal feeding.

A multicenter trial is ongoing under the direction of the Dutch pancreatitis group.[76] The design of this study is to enroll patients with predicted SAP based on APACHE scoring, Imrie score, and CRP. The patients will be randomized to nasojejunal feeding within 24 hours of admission or routine feeding with oral feeding at 72 hours, vs nasojejunal tube feeding. The end point will be mortality and infection-related complications. The results of this study will be very interesting because they will drive the use of EN in patients with SAP.

At this time, the recommendations are to use EN rather than PN. It is reasonable to use oral feeding if the patient can tolerate this. Gastric and jejunal feeding are likely equivalent. Certainly, every effort should be made to use the GI tract over PN. Probiotic supplements may be beneficial.[77]

*Abdominal compartment syndrome*

In the patient with SAP and multiorgan failure in the early phase requiring aggressive volume resuscitation, the question of abdominal compartment syndrome (ACS) may arise. The general definitions of ACS apply. This condition is defined as "persistent abdominal pressure more than 20 mm Hg accompanied by new onset organ failure."[78] As the reader can imagine, this may in fact be more common than thought in the patient with SAP who requires aggressive volume resuscitation, develops acute kidney injury, and requires intubation. De facto, many of the patients with SAP who have multiorgan failure would potentially meet criteria for ACS. Although decompressive laparotomy benefits patients with trauma who develop ACS, the data on SAP are not clear.[79] The etiology of ACS in the patient with SAP is different than in the usual surgical patient, in that fluid is sequestered into the retroperitoneum and the volume of fluid that is required to cause ACS is more an indicator of the severity of the disease itself. As such, all measures must be taken to avoid decompressive laparotomy in the patient with SAP.[80] Measures such as paralysis, catheter drainage of ascites, diuresis if possible, and ventilator measures can aid in decreasing abdominal pressures.[81] Rarely, in the patient with acute pancreatitis who is declining even with all of these measures, decompressive laparotomy is required; this may even be undertaken at the bedside in the critically ill patient who is too sick for transportation. The surgeon should try to avoid this at all costs because the outcome may not be altered by decompressive laparotomy.

*Subacute phase—weeks 2 and 3*

Once the patient with acute pancreatitis has made it past the first week of treatment, it is clear which group they are going to fall into: (1) those who are critically ill and have developed multiorgan failure, (2) those who have developed multiorgan failure which is improving, or (3) those who developed transient multiorgan failure that has resolved

The patients in the latter 2 groups can be advanced on their oral intake and can often be discharged to home with close follow-up. Treatment may still be required for WOPN with time if the patient is symptomatic.

The main question in this phase of treatment is whether the patient has developed infected pancreatic necrosis. The diagnostic dilemma is whether the patient has infected necrosis or

sterile necrosis. Intervention for sterile necrosis is not recommended at this time because it does not improve the outcome.[4] The important paradigm is that cross-sectional imaging, usually dedicated CT scan with pancreas protocol IV contrast administration, is critical in defining the treatment pathway chosen for these patients. In general, the recommendations are moving away from early CT (unless there is a question of diagnosis) to using CT at this subacute phase of acute pancreatitis.[46] The concept is that this will decrease cost and radiation exposure and more accurately diagnose patients that will need intervention. It is noteworthy that the percentage of necrosis that is seen on CT scan will predict the likelihood of developing infected necrosis. Those with less than 30% necrosis will have a lower chance of developing infected necrosis (22.5%) than those with greater than 50% necrosis (46.5% risk of infected necrosis).[30] This latter group is the group that will need careful monitoring in this subacute phase of acute pancreatitis.

*Role of FNA*

FNA was a commonly used technique in the last few years. The aim of FNA is to aspirate the pancreas and document infection.[26,82] If this is documented, some intervention is necessary—either percutaneous drainage or surgery. These patients are very ill, and the older dictum of early surgery has really been challenged. The authors who trained in that era remember many extremely sick patients with SAP that seemed to do worse with surgical debridement.

The current role of FNA has diminished tremendously.[32] Patients who have no indication of infection on imaging and are gradually improving are not good candidates for FNA as the information will not change the clinical plan. The patient who has gas in the peripancreatic tissues or acute PFC does not need an FNA as they clearly have infection and need an intervention. The patient who is either not improving over time with no imaging findings of overt infection, or is deteriorating despite no clear evidence for infection on imaging will benefit from FNA. This latter group is actually the minority of patients with SAP. The common question is whether the latter patient with an acute peripancreatic fluid collections would actually be considered for drainage regardless of the FNA result.[83] Many times, in the patient who has a clinical picture that is not improving, or deteriorating, placement of a drain into the fluid collection is considered in an attempt to improve their clinical course.

An interesting retrospective study looked at patients with SAP who were subjected to liberal FNA with surgery for FNA-positive patients, compared with a conservative treatment plan where patients were followed up prospectively.[32] Of 24 patients, 10 in the latter group required surgery for extrapancreatic complications. The mortality rate in the routine FNA groups was 45% compared with 8% in the conservatively treated group. Although there are many concerns with the design of this study, with a significant type II inherent bias, the data suggest that routine FNA is not indicated in patients with acute pancreatitis.

In summary, FNA is not recommended on a routine basis in patients with SAP. FNA should be reserved for patients in whom the clinical pathway will be altered by a definitive diagnosis of infected necrosis. If the result of the FNA is positive, intervention using one of the measures outlined later will be necessary.

*Nutrition*

As in the acute phase, nutrition becomes a key factor in recovery from severe pancreatitis. Similar to the data presented earlier, EN is superior to PN.[73] In general, oral intake is encouraged if the patient can tolerate a diet without nausea, emesis, or increasing abdominal pain. A low-fat diet can be used to decrease pancreatic stimulation and decrease the risk of biliary issues.[84]

Patients with severe pancreatitis may, however, develop an ileus or delayed gastric emptying owing to inflammation and fluid behind the stomach. In this case, it may be necessary to place a feeding tube distal to the pylorus to bypass the stomach. Data would suggest that nasogastric and nasojejunal feeding are equivalent.[74] The historical concept was that feeding distal to the pancreas might result in decreased pancreatic stimulation and therefore decreased risk of aggravating the SAP.[74] Although a good prospective study is still underway, at this time it is recommended that the GI tract be used in any way possible to feed the patient.

In the patient who is not tolerating enteral feeds at all, the treating physician should try trophic tube feeds at least, to maintain gut permeability.[73] Calories will have to be delivered parenterally in this case. The main cause for concern with TPN is related to hyperglycemia and sepsis related to line infection.

*Supportive care*

Patients with SAP may be on a ventilator at this time, and routine ventilator weaning trials should be undertaken. The mode of ventilator weaning is not discussed here, but there are several guideline documents that can provide excellent data.[1,85,86] Tracheostomy should be considered in those patients who do not appear to be readily liberated from the ventilator.

Physical therapy and mobilization should be an area of focus in these patients that are ill in the ICU. Passive range of motion, change of position, and attention to pressure points are all part of the treatment plan. Occupational therapy must be included in this phase of treatment.

*Delayed phase—weeks 3-6*

In this more chronic phase of care for the patient with SAP, the main concern focuses on how to treat the fluid collections and necrosis that develop. The definition of these fluid collections, as described in the 2012 revised Atlanta classification, is critical as the patient moves into the next phase of treatment.

*Role of imaging*

The primary diagnostic modality is CT scan to evaluate fluid collections and to define the extent of necrosis. MRI may be used in these patients. CT has the benefits of smaller slice thickness, has the ability to do dynamic phase imaging to evaluate necrosis more effectively, has the ability to use images to plane interventional radiologic (IR) interventions, is better able to delineate air on CT scan than MRI, and the patient must lay still for a shorter period of time. MRI has the benefits of no radiation, the ability to visualize and define the pancreatic and bile ducts without intravenous contrast (can be seen well on T2-weighted imaging), and the ability to delineate fluid from necrotic material or pseudocyst from WOPN.

In general, CT scan is used as the first test of choice in evaluating the patient with SAP in this delayed phase. The decision to intervene (described later) is mostly made on the basis of the CT imaging and symptomatology. MRI and MRCP are used to evaluate the extent of solid debris within the fluid collection and to evaluate the pancreatic duct to ascertain whether the patient has a "disconnected duct."[52] With this latter entity, there is a disruption of the pancreatic duct owing to SAP. Therefore, there is a portion of pancreas that is to the patient's left that does not drain effectively.

*Role of EUS*

EUS has been most commonly used to evaluate and biopsy pancreatic masses, including cysts and solid tumors.[87] The role of EUS has been examined in patients with both acute and chronic pancreatitis. A study examined the role of EUS compared with that of MRCP in determining the need for ERCP in patients that presented with biliary pancreatitis.[88] The authors found that EUS had a similar ability to MRCP in determining the need for ERCP. It is noteworthy that these patients had mild to moderate, rather than severe, biliary pancreatitis.

Another study reviewed the role of EUS in patients with acute pancreatitis.[56] The authors suggest that EUS should be performed before ERCP in all patients being evaluated for ERCP. In a study, 5 of 6 patients with suspected biliary pancreatitis would be saved the risk of ERCP if EUS was performed before ERCP.[89] EUS was also found to be very sensitive for detection of sludge in patients with a negative finding on transabdominal US image and idiopathic pancreatitis. Detection of sludge or microlithiasis by EUS was noted in 33 of 35 patients with a negative

finding on transabdominal US image.[90] The authors of this report found that cholecystectomy relieved symptoms in these patients with findings only on EUS, suggesting that sludge or microlithiasis was the cause of acute pancreatitis of unknown etiology.

Pancreas divisum is a cause of pancreatitis that can be detected on EUS.[56] This diagnosis can then be used to trigger ERCP and possible measures to improve drainage.[91]

EUS can be used to evaluate WOPN in the patient who is in this delayed phase of SAP. EUS is excellent at delineating fluid from necrotic debris.[92,93] The main role of EUS in this circumstance is to direct the primary modality required for subsequent intervention. The EUS determines whether there is simple fluid or whether there is necrosis within the fluid. This modality can be useful in assessing the patient that may be a candidate for percutaneous drainage alone, as opposed to open necrosectomy. EUS is also essential in defining the fluid collection and the mode of access in those who are being considered for endoscopic drainage procedures.

*Open necrosectomy*

Historically, patients with infected pancreatic necrosis or suspected infection were subjected to open pancreatic debridement.[94] The traditional approach is via a bilateral subcostal approach, entry into the lesser sac reflecting the stomach toward the head and the colon toward the feet, and debridement of the retroperitoneum.[95] Those with experience in this procedure understand the importance of gently teasing out the pancreatic debris without violating the vascular structures that meander through these areas (eg, superior mesenteric vein and artery, splenic artery, and splenic vein). An example of the material that can be retrieved from the retroperitoneum is shown in Figure 11. A method that has worked for the authors is to use a ring forceps to retrieve these necrotic products. A discerning finger can also loosen up contents well, together with aggressive use of saline irrigation into the lesser sac. Care must be taken to avoid mobilization of the splenic flexure of the colon, as there is often associated venous thrombosis and loss of collaterals with mobilization can result in colonic congestion and ischemia. Care must be taken to avoid entry into the medial wall of the duodenum, posterior wall of the stomach, or transverse colon as one loosens the pancreatic necrosis. Visualization of bile should lead the surgeon to investigate a medial duodenal fistula; generally, nothing can be done for this finding except wide drainage. In general, these fistulae will close with time.[96]

After necrosectomy, drains are laid in the retroperitoneum and there are some groups that advocate continuous lavage for 5 days postoperatively.[97] This is thought to continue drainage and evacuation of debris. The surgeon can consider placement of a feeding jejunal tube at the time of open necrosectomy as needed. Data would suggest that patients will need to return to the operating room for further debridement after open necrosectomy. Overall, 31% of the open necrosectomy patients required more than 2 trips to the operating room in the Pancreatitis, Necrosectomy vs Step-Up Approach trial.[98,99] The authors have found that return to the operating room is rarely needed in their experience with aggressive, primary open necrosectomy in the patient with SAP and infected necrosis.[100] This is a difficult decision to make, as the patient that falls into the group is often critically ill and may display signs of ongoing SIRS. The decision to return to the operating room is made on the following grounds in our experience: (1) progressive multiorgan failure despite apparently adequate drainage; (2) inadequate drainage or retained necrotic material on abdominal imaging, generally the CT scan; or (3) concern for other missed pathology, specifically ischemic bowel or bowel perforation.

Again, the patient with infected pancreatic necrosis can be a diagnostic dilemma, and the decision to return to the operating room is a very personal and experience-driven one.

The alternative approach that can work well in the more delayed circumstance is the retroperitoneal approach, usually through the left flank.[101] This approach is best performed with the patient in decubitus position with the left side up. An incision can be made similar to a retroperitoneal approach to an abdominal aortic aneurysm and the retroperitoneum can be debrided without entering the abdomen.[102] This is very advantageous.

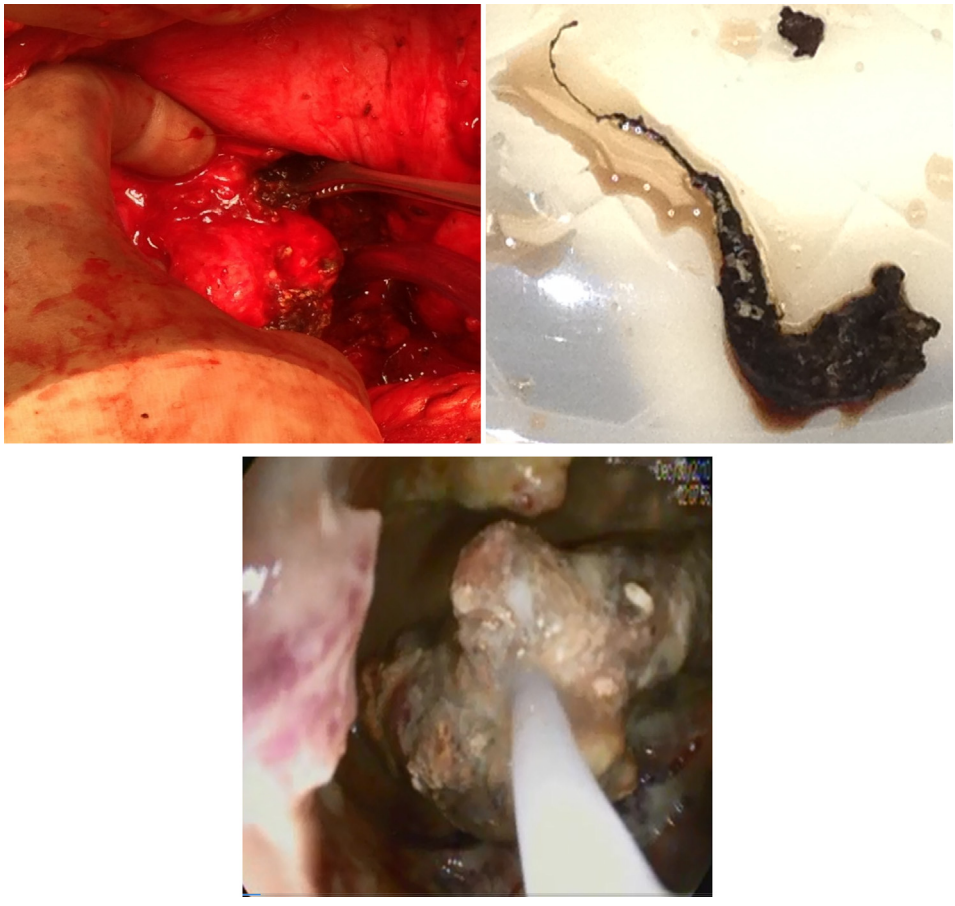

**Fig. 11.** Necrosectomy performed through open surgical approach (upper panels) and endoscopically (lower panels). (Color version of figure is available online.)

*Percutaneous drainage*

The advent of aggressive IR maneuvers to drain PFCs has been a significant advance in the field of acute pancreatitis. Historically, the inability to achieve drainage via IR routes has led to open surgery. In the current era, most fluid collections can be targeted using US or CT scan planning[103,104] (Fig 12). The field has become so sophisticated that we now ask the interventional radiologist for a specific route of placement of drains. In light of the "step-up" approach (described later), where there may be future use of the drains to direct minimally invasive necrosectomy, it is advantageous to place drains via a retroperitoneal approach.[105] This may not be possible in those patients with collections that are centrally located with minimal left retroperitoneal extension (Fig 13). In these cases, the radiologist should be asked to place drains in any manner that will achieve adequate drainage.

In general, a large drain should be placed into the collections. However, most interventional radiologists will start with a small drain (12 F) and then upsize the drain gradually to a 20-F drain or larger. It is the role of the surgeon to mandate frequent upsizing to ensure that adequate drainage is achieved.

There has been much controversy about whether percutaneous drainage alone can suffice in treating infected necrosis and WOPN.[106] The argument against percutaneous drainage alone has centered on the fact that the infected necrotic solid tissue is not really drained with percutaneous

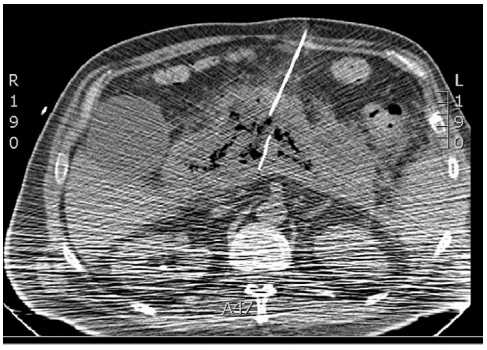


**Fig. 12.** CT-guided drainage of infected pancreatic necrosis.

drainage alone.[106] Many pancreatic surgeons feel that removal of the necrotic debris in infected necrosis is a critical measure in resolving SAP and multiorgan failure that accompanies this disease. Data from the Dutch pancreatitis trial found that 40% of patients in the percutaneous drainage arm required no surgical intervention.[107] The Horvath video-guided retroperitoneal drainage (VARD) study found that 23% of patients could be treated with percutaneous drainage alone without further surgical intervention.[108] A meta-analysis published by Mouli and colleagues[58] looked at the published literature from 1990-2012. The authors specifically examined the role of conservative management to those that needed surgical debridement; they found that in those studies that used percutaneous drainage in all of their patients, this modality alone was successful in 47%-63% of patients treated.[109] A study by Solanki and colleagues examined factors that predict failure of percutaneous drainage. These authors found a higher APACHE score and the presence of greater than 50% pancreatic necrosis was associated with the need for further debridement and the failure of percutaneous drainage alone.[110] These data would suggest that drainage of fluid with aggressive flushing and lavage of loose debris can achieve adequate resolution of multiorgan failure and sepsis in patients with infected necrosis. These data are contrary to the popular notion that some form of debridement is required in patients with infected necrosis and WOPN.

Our experience is that the number of patients who require surgical debridement is actually smaller than the reported number. We believe that this is owing to an aggressive IR-guided approach in these patients with aggressive upsizing of drains. Large 28-F chest tubes in the retroperitoneum can be placed when there are no drains of adequate size in specific circumstances. We generally will not place drains to wall suction but will keep these drains to bulb suction rather than passive gravity drainage. Flushing of drains is generally performed with 30 mL of sterile saline via a 3-way stopcock that is built into the drainage circuit. A study that

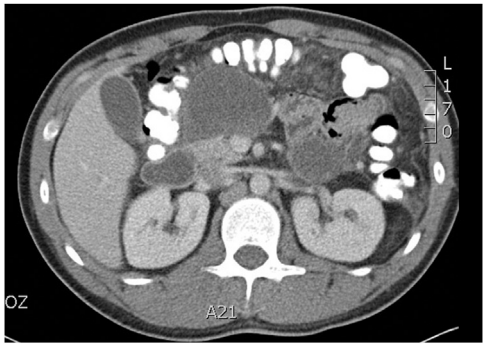


**Fig. 13.** Enhanced CT scan with central walled-off pancreatic necrosis unamenable to left retroperitoneal percutaneous approach.

examined the instance of resolution of peripancreatic fluid collections found that with aggressive upsizing of drains and placement of multiple drains, resolution of collections occurred in 84% of patients.[103] This experience is more reflective of our own.

In summary, percutaneous drainage can be used to treat acute peripancreatic fluid collections and WOPN in patients with SAP. There are specific instances in which percutaneous drainage alone will suffice in resolution of acute peripancreatic fluid collections. There is no empiric need for debridement of acute pancreatic necrosis even in the face of infected necrosis. This is contrary to the traditional belief that all infected necrosis necessitated necrosectomy. The decision to proceed to further surgical intervention should be made on clinical grounds.

*Endoscopic drainage*

The use of endoscopic drainage was popularized in the late 2000s but has decreased in popularity with the advent of a more organized "step-up" approach. The principle of endoscopic management is to define the collection as either fluid filled or WOPN.[111] The fluid-filled collections can be targeted via a gastric approach with EUS. Briefly, the endoscope is placed into the stomach and EUS is performed. A plane with excellent opposition of the stomach wall to the cyst is found and a puncture is made into the cyst.[112] The tract is dilated and several stents are placed across this connection to facilitate drainage of fluid from the pancreatic cyst.[112] In general, this maneuver alone is used in patients who meet the following criteria: (1) late in the phase of disease ( $>6$ weeks after onset of acute pancreatitis); (2) fluid collection with minimal to no necrosis associated with it (best defined by MRI and EUS, the modalities that can delineate pancreatic necrosis from fluid better than CT scan); (3) excellent opposition of the stomach to the cyst wall; (4) no gastric varices that may cause bleeding at the time of puncture and dilation; and (5) patients' ability to withstand endoscopy.

As can be surmised from the patients' characteristics mentioned earlier, there are specific candidates for primary endoscopic drainage. The patients that fall into this group tend not to be critically ill, temporally distant from their episode of SAP, and radiographically amenable to endoscopic therapy. In practice, this is a small group of patients.

Patients with WOPN can be treated endoscopically with endoscopic necrosectomy. In this circumstance, the tract across the stomach into the fluid collection is dilated and an expandable stent is placed. The endoscope is then placed into the fluid collection and mechanical debridement is performed using various endoscopic tools such as baskets and forceps.[113] A nasogastric tube is generally placed across the stomach into the area of WOPN and flushed aggressively with saline to debride this area mechanically and loosen any debris.

*Dual (endoscopic and percutaneous) modality drainage*

The use of endoscopic and percutaneous drainage was popularized by the Virginia Mason group.[114] The authors retrospectively examined a cohort of patients that received dual-modality drainage (DMD) or standard percutaneous drainage (SPD). In total, 49 patients in the surgeon-monitored sedation group were compared with 46 patients in the SPD group. The idea behind DMD was to place a drain into the PFC and then place a stent across the stomach into the PFC. Flushing the percutaneous drain aggressively was postulated to loosen up debris and result in efflux into the stomach through a large endoscopically created connection (Fig 14). The length of stay, number of procedures needed, number of CT scans required, and the time to removal of drains were significantly decreased in the DMD group compared with the SPD group. The 30-day mortality rate was 4% in the DMD group compared with that of 7% in the SPD group. None of the patients in the DMD group required operation, whereas 6% in the SPD group required operation.

Although the data from this study are very compelling, a closer look at the mortality numbers would suggest that the patients included in this study were in fact not critically ill. The expected mortality in patients with SAP and infected necrosis is reported as at least 30% in many studies.[114] Therefore, the excellent results noted in this study would suggest that patient selection may play a critical role in those that are identified as candidates for the DMD approach. An issue that has been raised is the concern for creation of a gastrocutaneous fistula. This was

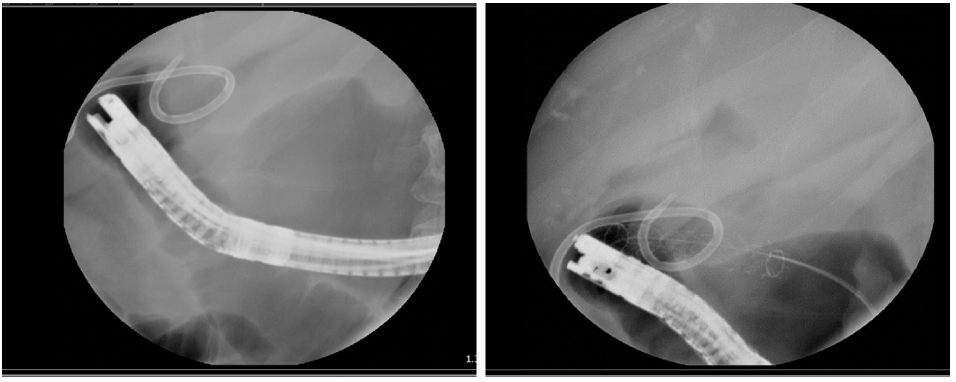

**Fig. 14.** Dual drainage via endocsopic and percutaneous approach of a walled-off pancreatric necrosis.

not noted in this study, although this complication has been encountered by our group. In these cases, removal of the endoscopically placed stent can resolve the issue.

At this time, DMD is a modality that can be considered in patients with WOPN and infected necrosis. This modality should be reserved for those patients who are not ill and have the ability to withstand endoscopic procedures. This mode of drainage is intriguing and should be considered in the modalities available for patients with WOPN and peripancreatic fluid collections.

*Video-guided retroperitoneal drainage*

The use of minimally invasive techniques to debride and drain peripancreatic fluid collections and WOPN was popularized at the University of Washington by Horvath and colleagues.[108] The concept was that the retroperitoneum could be accessed by following drains that had been placed by the interventional radiologist and debridement of this space could be performed using large bore trocars.[115] Laparoscopic cameras and instruments can be used through 1 large (generally thoracoscopic-type) trocar, or alternatively several trocars can be placed into the peripancreatic fluid collection. Thereafter, laparoscopic instruments can be used to carefully debride the retroperitoneum.[115] Care must be taken not to disrupt vital structures such as the splenic artery or superior mesenteric vein. This can be difficult and it is the advice of the authors to err on the side of being conservative rather than aggressive, with the understanding that repeated procedures may be required. Drains are then replaced and flushing can be performed to evacuate further debris that can efflux through the drains.

A prospective, multicenter study was performed by this group and included 40 patients with SAP.[115] It is noteworthy that the mean APACHE score was 8 in the cohort, which suggests that these were in fact not critically ill patients. The authors examined the role of VARD in patients with infected pancreatic necrosis, documented or suspected. The first finding was that SPD alone resulted in a greater than 75% decrease in peripancreatic fluid collections in 23%. This was an unexpected finding for the authors, as they had planned the study assuming that SPD was just a step to VARD. In fact, 23% of patients did not need to go on to further surgical intervention.

Of those patients that required further intervention, 60% were found to be candidates for VARD. Those unable to undergo VARD were excluded owing to inability to access the retroperitoneum through the drains placed, or concern for other pathology such as ischemic bowel or bowel perforation. The major predictor for failure of VARD was the presence of a medial pancreatic fluid collection that could not be well drained from the flank. These patients were found to be better accessed by endoscopic drainage, percutaneous drainage, or open pancreatic drainage.[116]

In summary, the use of VARD can be contemplated in patients who are not overly ill, who have retroperitoneally accessible fluid collections, and who do not have medial extension of fluid collections into the mesentery. This technique should be used as a modality for the “step-up” approach outlined later.

*"Step-up" approach*

The culmination of all of the approaches outlined earlier has led to the "step-up" approach for the management of infected necrosis and WOPN. The main theme is to use minimally invasive measures first with a gradual progression to more invasive techniques.

At presentation, the patient with SAP should be managed as outlined earlier. The supportive care should include aggressive fluid resuscitation, enteral feeding wherever possible, and ventilator support as needed, along with other medical management. Antibiotics should be used sparingly. Progression of multiorgan failure and development of infected necrosis should drive the managing surgeon to evoke the next phase of the "step-up" approach. This will require placement of percutaneous drains into peripancreatic fluid collections. Drains should be placed via a retroperitoneal access if at all possible, to allow for VARD if this is needed in the future. The placement of drains should be delayed as much as possible with the intent to wait at least 4 weeks before this intervention.[108] The aim here is to have peripancreatic fluid collections or WOPN that are walled off and are able to be drained effectively. Drains should then be up-sized frequently to at least a 20-F drain. The surgeon should coordinate these serial up-sizings of drains with the interventional radiologist. This team approach to the patient with SAP is critical in the management of these extremely ill patients. The surgeon is the one that is ultimately responsible and will have to intervene if there is failure of the percutaneous measures; therefore, it is in the surgeon's best interest to get involved at an early time point in the treatment of these patients.

Factors that have been associated with a lack of success of percutaneous drainage alone have been[117]: (1) lack of decrease in the size of peripancreatic fluid collections by $>75\%$ in 1 week, (2) $>50\%$ pancreatic necrosis on CT scan, (3) high APACHE score at time of drainage ($>7.5$), (4) renal failure, and (5) multiple organisms in drainage fluid.

Although percutaneous drainage should be used as the first step in the "step-up" approach even in patients with poor prognostic factors for resolution with drainage alone, the surgeon should understand that these patients will have a high likelihood of requiring further intervention usually with surgery.

Failure of percutaneous drainage alone with aggressive up-sizing of drains should lead to the next phase of the "step-up" approach; this will be surgical intervention of some type. Options include the following: (1) VARD, (2) DMD, (3) endoscopic drainage, (4) endoscopic necrosectomy, or (5) open necrosectomy.

The choice of which modality to use is dependent on the comfort level of the surgeon, interventional radiologist, and interventional gastroenterologist. In general, it is beneficial for these patients with SAP to be treated at a center where all of these service lines are available. Open surgical necrosectomy is an appropriate treatment if other modalities are not available at a specific institution and is still an effective treatment modality for infected necrosis. Many studies have demonstrated differences in complications with open surgical necrosectomy compared with other techniques.[108,118,119] However, the overall mortality rate is similar with all modalities and open necrosectomy can be used when other techniques are not available or expertise in other modalities is not available. Most studies comparing open surgery with other modalities are plagued with selection bias. The surgical patients are the sickest patients in these studies with the highest expected mortality.[118] Intervention should be delayed as long as can be tolerated.[25]

Optimal management should include VARD when percutaneous drainage has not been shown to be effective. The decision to proceed to further "step-up" approaches should be based on clinical measures and not solely on radiographic measures. For example, if the patient is doing very well, eating and not displaying any signs of multiorgan failure or SIRS, despite an ongoing peripancreatic fluid collections or acute necrotic collections, it is reasonable to continue to monitor this patient and treat him or her expectantly. However, if the patient is declining despite what appears to be effective percutaneous drainage, consideration should be given to VARD or necrosectomy of some kind.

The choice of "step-up" technique should be based on the experience of the team. When there is expertise in the area of gastroenterological drainage, DMD may be considered. When there is expertise in minimally invasive surgery, VARD may be the preferred approach in the

next step up. The treating surgeon should remember that the percutaneous approach alone may be enough to control sepsis and reverse multiorgan failure in the patient with infected necrosis.[24,108] "Step up" to the next technique should be invoked only when there are clinical indications that aggressive percutaneous drainage alone is not working.

There should be a specific plan for the treatment of the patient with SAP and infected necrosis. This should include medical management, placement of drains, and then surgical intervention as dictated by the patient's clinical course. The modality of surgical intervention should be dictated by the comfort level of the surgeon and gastroenterologist.[97] Open necrosectomy should be reserved for failure of other less invasive techniques to address infected necrosis.[120]

In summary, acute pancreatitis is a serious illness that can result in a high rate of mortality. Initial resuscitation is a key element of treatment of this disease. Progression to multiorgan failure can occur, usually within the first 48 hours, and portends a different clinical course than for the patient with mild acute pancreatitis. Antibiotics should be withheld and early enteral feeding should be encouraged. Intervention for infected pancreatic necrosis should be based on a "step-up" approach using percutaneous drainage and then up-sizing drains and possibly VARD. Open surgery should be reserved for failure of less invasive techniques but should certainly be utilized and must be within the skill set of the treating surgeon.

Acute pancreatitis is a disease that requires involvement of multiple specialties, including gastroenterologists, surgeons, intensivists, and interventional radiologists. The team is critical to the successful treatment of these patients.

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