

## AGA Institute Technical Review on Acute Pancreatitis

### CME quiz on page 2002.

Acute pancreatitis remains a disease characterized by significant morbidity and mortality, with several reports noting an increasing annual incidence of disease.<sup>1</sup> Clinical practice position papers, such as this one, are designed to educate and guide physicians in patient care decisions. These guidelines attempt to summarize the best available data and to describe best clinical practice. It is worthwhile to state directly that this approach is somewhat limited in the area of acute pancreatitis, owing to the relative paucity of large randomized controlled trials. Guidelines such as these, in the absence of this type of supporting scientific proof, must include a healthy measure of less solid evidence-based recommendations, including a wealth of expert opinion. It is certainly possible that future large randomized trials might lead to changes in yet-to-be-written guidelines similar to this one. Acute pancreatitis is a disease of such variability that it cannot be effectively managed by following blindly any set of recommendations, and these guidelines are not intended as tantamount to the legal standard of care. Rather, it is hoped this position paper can combine the available scientific studies and evidence base (or lack thereof) with expert opinion into a useful tool for clinicians.

### Diagnosis

The diagnosis of acute pancreatitis is usually suspected based on compatible clinical features including abdominal pain, nausea, and vomiting. It has been estimated that in 40%–70% of patients, the classic pattern of pain radiation to the back is present. Pain usually reaches its peak over 30–60 minutes and persists for days or weeks. It is clear that not all patients may experience pain, or alternatively that the presence of pain may not be appreciated by the clinician caring for the patient. Several retrospective analyses of fatal acute pancreatitis have noted that in 30%–40% of patients, the diagnosis of acute pancreatitis was only made at autopsy.<sup>2–4</sup> The diagnosis of acute pancreatitis was not suspected in these patients because abdominal pain was not present or because other clinical symptoms (eg, coma or multiorgan system failure) dominated the clinical picture. In some of these patients, the serum amylase level was also normal or only minimally elevated.

The clinical suspicion of acute pancreatitis is supported by the finding of elevations in serum amylase and/or lipase levels. Measurement of amylase is more widely used. The pancreas is responsible for about 40% of total serum amylase, with the rest originating primarily in the salivary

glands. Elevations in total serum amylase are therefore not specific for pancreatitis, and a number of other intra-abdominal conditions should be considered (Table 1). Most textbooks and most expert opinions suggest a level of at least 3 times the upper limit of normal as the most accurate cutoff. In one prospective analysis of 500 patients presenting to an emergency department with acute abdominal pain, the sensitivity of serum amylase estimation was 85%, with a specificity of 91%.<sup>5</sup> A retrospective analysis of 95 patients with nonpancreatic abdominal pain and 75 patients with acute pancreatitis estimated a sensitivity for serum amylase of 72% and specificity of 99%.<sup>6</sup> A prospective analysis of serum amylase measurements at a single hospital over 3 years noted a sensitivity of 45% and a specificity of 97%, using a post-hoc diagnostic threshold of 176 U/L (about 2 times the upper limit of normal).<sup>7</sup> Serum amylase is hampered as a diagnostic tool by the fact that elevations may not occur (or be missed, depending on the timing of collection of serum) in mild attacks, in acute flares superimposed on chronic pancreatitis (especially chronic alcoholic pancreatitis), and in some patients with marked hypertriglyceridemia (elevated triglyceride levels can interfere with the assay). Amylase may be falsely elevated in several nonpancreatic conditions, including renal insufficiency and macroamylasemia.

Elevation in serum lipase is purported to be more specific than that of amylase for the diagnosis of acute pancreatitis. The widespread use of lipase in the past was prevented by the difficulty in precise measurement of lipase on commercially available analyzers. This is generally no longer the case, but there may still be variability in local laboratory methods of analysis. Superior specificity can likely be explained by the fact that there are no other significant sources of lipase that reach the serum. Lipase may also be slightly more sensitive than amylase, owing to the fact that it remains elevated in the serum longer than amylase.<sup>8</sup> In one study noted previously,<sup>6</sup> the sensitivity of lipase was 100% and the specificity was 96%, compared with 72% and

*Abbreviations used in this paper:* APACHE, Acute Physiology and Chronic Health Evaluation; CECT, contrast-enhanced computed tomographic scan; CI, confidence interval; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; ICU, intensive care unit; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; SIRS, systemic inflammatory response syndrome; SOD, sphincter of Oddi dysfunction; TPN, total parenteral nutrition.

**Table 1.** Causes of Increased Amylase and Lipase Levels

Amylase	Lipase
Acute pancreatitis	Acute pancreatitis
Diseases that might mimic acute pancreatitis	
Pancreatic pseudocyst	Pancreatic pseudocyst
Chronic pancreatitis	Chronic pancreatitis
Pancreatic carcinoma	Pancreatic carcinoma
Biliary tract disease (cholecystitis, cholangitis, choledocholithiasis)	Biliary tract disease (cholecystitis, cholangitis, choledocholithiasis)
Intestinal obstruction, pseudo-obstruction, ischemia, or perforation	Intestinal obstruction, pseudo-obstruction, ischemia, or perforation
Acute appendicitis	Acute appendicitis
Ectopic pregnancy	
Other disorders	
Renal failure	Renal failure
Parotitis	
Macroamylasemia	
Ovarian cyst or cystic neoplasm	
Carcinoma of the lung	
Diabetic ketoacidosis	
Human immunodeficiency virus infection	
Head trauma with intracranial bleeding	

99%, respectively, for amylase. These results for lipase are impressive, but other studies have noted sensitivities ranging as low as 55% using a cutoff of 3 times the upper limit of normal.<sup>9</sup> Some studies that show superior specificity of serum lipase compared with amylase used less reliable methods of lipase determination than are currently used,<sup>10</sup> but some modern studies also note better specificity.<sup>11</sup> Lipase may also be elevated in certain conditions that might mimic acute pancreatitis (Table 1) and in the setting of renal insufficiency. Both serum amylase and lipase may be elevated in patients with renal insufficiency due to decreased clearance. At a creatinine clearance between 13 and 39 mL/min, amylase is elevated in somewhat more than half of patients and lipase is only elevated in approximately one fourth of patients,<sup>12</sup> suggesting an additional advantage for lipase. There are no data that measuring both amylase and lipase adds significant diagnostic accuracy. Once the diagnosis is established, measuring either amylase or lipase on a daily basis has little value in gauging clinical progress or prognosis.

A variety of other pancreatic enzymes can be measured in serum or urine and might have utility as a diagnostic tool. These include pancreatic isoamylase, phospholipase A<sub>2</sub>, elastase 1, anionic trypsinogen (trypsinogen-2), and others.<sup>13</sup> Although some studies have shown impressive results,<sup>5</sup> these tests have not become available for routine clinical use.

The lack of specificity of both amylase and lipase as diagnostic tests implies that these can be used to support the diagnosis of acute pancreatitis but may not definitively provide a secure diagnosis, particularly if the levels are not dramatically elevated. The diagnosis of acute pancreatitis, if in doubt, is best corroborated by imaging tests, particularly computed tomography (CT).

Transabdominal ultrasonography is not able to image the pancreas in a substantial number of patients with acute pancreatitis, often due to overlying bowel gas. Ultrasonography is not accurate at identifying necrosis of the gland or in accurately assessing the severity of peripancreatic inflammation and fluid. The primary role of abdominal ultrasonography in patients with acute pancreatitis is to identify gallstones or dilation of the common bile duct due to choledocholithiasis. The sensitivity of transabdominal ultrasonography to detect gallstones in patients with acute biliary pancreatitis is about 70%.<sup>14</sup> Some studies have noted that repeating ultrasonography after recovery increases the yield for identifying gallstones.<sup>15</sup>

The role of CT in patients with acute pancreatitis can be to confirm the diagnosis, exclude alternative diagnoses, determine severity, and identify complications. It has been stated that 15%–30% of patients with mild pancreatitis may have a normal CT scan.<sup>16,17</sup> This opinion is not able to be directly corroborated, because CT is often used as the gold standard for the confirmation of acute pancreatitis. Presumably, multidetector CT utilizing a pancreas protocol will have improved diagnostic accuracy, because it has improved accuracy to detect severity and complications.<sup>18</sup> CT findings of acute pancreatitis can range from isolated diffuse or focal enlargement of the gland to peripancreatic stranding and peripancreatic fluid collections and, at its most severe, pancreatic gland necrosis. Pancreatic necrosis is identified by the absence of enhancement of the pancreatic parenchyma after intravenous contrast administration (typically remaining <30 Hounsfield units after intravenous contrast) on a contrast-enhanced CT scan (CECT). Pancreatic necrosis may not be fully apparent on a CECT for up to 3 days after disease onset, and a very early CECT may underestimate the severity of pancreatitis. A recent concern has been the potential for intravenous contrast to impair pancreatic microcirculation and potentially aggravate the degree of pancreatic necrosis and worsen the course of acute pancreatitis.<sup>19,20</sup> This can be demonstrated in some, but not all, animal models. Several retrospective studies in humans noted that those patients who underwent a CECT seemed to have a worse outcome than those who did not, but these results may easily be explained by preexisting differences in severity in the 2 groups. The only randomized trial<sup>21</sup> showed no detrimental effect of CECT in patients with severe acute pancreatitis, but the number of patients in this study was too small to exclude a type II error. This topic has been recently reviewed,<sup>22</sup> but the evidence is not convincing that intravenous con-

trast worsens the severity of acute pancreatitis. Nonetheless, a CECT is not needed in all patients and, if not needed to confirm the diagnosis or exclude alternative diagnoses, can usually be delayed for 2–3 days after the onset of the attack to most accurately determine severity. CT without intravenous contrast may also be useful to exclude alternative causes of abdominal pain in patients with unexplained symptoms but is not able to quantify the degree of pancreatic necrosis.

Magnetic resonance imaging (MRI) with gadolinium enhancement is as accurate as CT in imaging the pancreas and staging the severity of acute pancreatitis, including documenting the degree of pancreatic necrosis.<sup>18,23–25</sup> It is more difficult, however, to perform MRI scanning in critically ill patients and hence CT is usually preferred.

Although a number of conditions may mimic the clinical features of acute pancreatitis and may even be associated with elevations in amylase and/or lipase levels, the combination of clinical features, laboratory tests, and imaging studies, if needed, should allow the diagnosis to be reliably made within 48 hours of admission. Lipase has some advantages over amylase and is preferred if the result is rapidly available. Clinicians should be attuned to the possibility of acute pancreatitis in patients presenting with atypical clinical features, particularly with altered mental status, organ system failure, or the systemic inflammatory response syndrome (SIRS).

### Assessment of Severity

The assessment of severity is one of the most important issues in the management of acute pancreatitis. Approximately 15%–20% of patients with acute pancreatitis will develop severe disease and follow a prolonged course, typically in the setting of pancreatic parenchymal necrosis. Patients with severe acute pancreatitis associated with SIRS typically have a prolonged hospital stay and are the ones most likely to die from their disease process. The ability to quantify severity of disease allows clinical studies to be compared. For clinicians, however, the ability to predict severe acute pancreatitis would be most helpful, allowing the managing physician to be proactive in management such as triage to an intensive care unit (ICU), vigorous fluid resuscitation, correction of metabolic abnormalities (eg, acidosis, hypocalcemia), and administration of therapies to reduce severity (if such therapies become available). A variety of predictive systems have been developed with the goal of assisting clinicians in predicting prognosis. These include measurement of markers in serum or urine, CT, and multiple factor scoring systems. Determining the utility of these predictive systems requires a clear definition of what constitutes severe disease. Death from acute pancreatitis is certainly a clear end point of severe disease, but only about 2%–3% of patients overall die from acute pancreatitis.<sup>26</sup> Most series from tertiary referral centers note mortality rates of 5%–15%,<sup>27–30</sup> but some go as high

as 30%. Approximately half the deaths occur in the first week due to multiorgan system failure.<sup>30</sup> Deaths after the first week are also usually due to multiorgan system failure but secondary to the development of infected pancreatic necrosis.<sup>31</sup> Other potential end points defining severe diseases include organ failure, extent of pancreatic necrosis, length of stay, need for ICU care or pancreatic surgery, cost, and others. There have been a variety of end points and definitions of severity used in various studies, making comparisons difficult. A widely accepted clinical classification of severity of acute pancreatitis appears in the proceedings of an international symposium held in Atlanta, Georgia, in September 1992.<sup>32</sup> In this document, severe acute pancreatitis was defined as the presence of organ failure and/or local pancreatic complications, complemented by the presence of unfavorable prognostic signs (using Ranson's criteria or Acute Physiology and Chronic Health Evaluation [APACHE] II). The definition included therefore both criteria that predict severe disease, along with the actual development of severe disease. Specific definitions of organ failure were adopted, including shock (systolic blood pressure <90 mm Hg), pulmonary insufficiency ( $\text{PaO}_2$  <60 mm Hg), renal failure (serum creatinine level >2 mg/dL), and gastrointestinal bleeding (>500-mL blood loss within 24 hours). Local pancreatic complications were defined as the development of a pseudocyst, abscess, or parenchymal necrosis (more than 30% or more than 3 cm of necrosis) (Table 2). Unfortunately, many of the primary studies that define the overall accuracy of various predictive systems were performed before the acceptance of these consensus definitions. Even many studies performed after the acceptance of these clinically based definitions of severity did not use the definitions correctly and instead developed new definitions of severity or modified the definitions from the Atlanta symposium. These factors limit the ability to compare systems that predict prognosis of acute pancreatitis.

The Atlanta criteria include unfavorable prognostic signs, either Ranson's criteria or APACHE II, in the definition of severe acute pancreatitis. The initial report of Ranson's criteria<sup>33</sup> was based on 100 patients (21 of whom underwent early surgery as part of a randomized trial or for uncertainty of diagnosis) (Table 3). The study identified 11 factors that predicted severe diseases (defined as death or an ICU stay beyond 7 days). The 11-point scoring system is measured in 2 stages: 5 initial data points on admission and a further 6 data points within the subsequent 48 hours. The initial report demonstrated a linear relationship between the number of criteria and the likelihood of mortality. Subsequently, modifications were made on the 11-point system for those with gallstone pancreatitis (the original studies were a mixture of alcoholic and biliary pancreatitis). These modifications reduced the number of criteria to 10 for those with gallstone pancreatitis.<sup>34</sup>

**Table 2.** Atlanta Criteria for Severity

Feature	
Organ failure	Shock (systolic blood pressure <90 mm Hg) Pulmonary insufficiency (Pao <sub>2</sub> <60 mm Hg) Renal failure (serum creatinine level >2 mg/dL after rehydration) Gastrointestinal bleeding (>500 mL/24 h)
Local complications	Pancreatic necrosis (more than 30% of the parenchyma or more than 3 cm) Pancreatic abscess (circumscribed collection of pus containing little or no pancreatic necrosis) Pancreatic pseudocyst (collection of pancreatic juice enclosed by a wall of fibrous tissue or granulation tissue)
Unfavorable prognostic signs	Ranson's score ≥3 APACHE II score ≥8

Adapted from Bradley.<sup>32</sup>

In the original publication, the sensitivity of 3 or more criteria to predict severe disease was 65% with a specificity of 99%, yielding a positive predictive value (PPV) of 95% and a negative predictive value (NPV) of 86%. Undoubtedly, the mortality of severe acute pancreatitis has progressively fallen with improvements in intensive care and the management of acid-base and other metabolic disorders and infection. Today, the overall mortality rate of acute pancreatitis is about 2%–3%,<sup>26</sup> versus about 15% in the initial report of Ranson's criteria. A meta-analysis of 12 published series using Ranson's criteria and encompassing 1307 patients reported an overall sensitivity for predicting severe acute pancreatitis of 75%, a specificity of 77%, a PPV of 49%, and an NPV of 91%.<sup>35</sup> These data highlight a very high false-positive rate of Ranson's criteria; many patients with a Ranson's score >3 will not develop clinically severe pancreatitis.

Ranson's criteria are cumbersome to use. If using both the gallstone and nongallstone criteria, 22 factors need to be remembered. It is also rare for all 11 Ranson's criteria to actually be measured; in an analysis at one of the authors' institutions (J. B.), on average only 8 were routinely available in retrospective chart review.

Another multiple factor scoring system was developed in Scotland and has become known as the Imrie or Glasgow criteria. The Glasgow criteria reduced the number of data points required to 8 (from 11). It was modified twice to improve the performance in patients with gallstone-induced acute pancreatitis.<sup>36–38</sup> The Glasgow criteria are utilized in areas of the world using SI units but not in the United States, despite an overall accuracy similar to the more complex Ranson's criteria.<sup>35</sup> Simpler scoring systems have been developed<sup>39,40</sup> but have not been validated.

One drawback of both Ranson's criteria and the Glasgow criteria is that they can only be determined after 48 hours, a fact that limits their usefulness as predictive systems. The APACHE II score provides equally useful

prognostic information and has the advantage of being able to be calculated at any time and to be recalculated as conditions change. The accuracy of prediction depends on the timing of calculating the APACHE II score and the cutoff chosen. Various studies have used APACHE II scores at admission, at 24 hours, and at 48 hours and have used cutoffs varying from 5 to 10. At admission, the sensitivity of an APACHE II score >7 to predict severe acute pancreatitis is 65%, with a specificity of 76%, a PPV of 43%, and an NPV of 89%.<sup>35</sup> At 48 hours, the sensitivity of an APACHE II score >7 to predict severe acute pancreatitis is 76%, with a specificity of 84%, a PPV of 54%, and an NPV of 93%.<sup>35</sup> Raising the cutoff to >9 improves the specificity and PPV but at a cost of less sensitivity and a reduced NPV.<sup>41–43</sup> A simplified APACHE II system called the Simplified Acute Physiology Score and a subsequent variation (Simplified Acute Physiology Score II, with “only” 17 variables) have been developed and validated in predicting prognosis in ICU patients.<sup>44</sup> Limited data in patients with acute pancreatitis suggest that these systems may be nearly as accurate as the APACHE II system.<sup>43</sup> A more complex system has also been developed (APACHE III) that incorporates an additional 5 physiologic factors, but this has not been fully validated in patients with acute pancreatitis.<sup>45</sup>

Other multiple factor scoring systems continue to be developed.<sup>46,47</sup> The judgment of an experienced clinician can also be used to estimate prognosis. The factors that a clinician might use to gauge severity vary but might include age, comorbid medical or surgical conditions, vital signs, urine output, body mass index, presence of rebound tenderness or guarding, delirium, abdominal wall or flank bruising, and the results of radiographic studies or a variety of laboratory tests (eg, oxygen satu-

**Table 3.** Ranson's Criteria

At admission	Within next 48 hours
Age older than 55 years (older than 70 years)	Decrease in hematocrit by >10% (same)
White blood cell count >16,000/ $\mu$ L (>18,000/ $\mu$ L)	Estimated fluid sequestration of >6 L (>4 L)
Blood glucose level >200 mg/dL (>220 mg/dL)	Serum calcium level <8.0 mg/dL (same)
Serum lactate dehydrogenase level >350 IU/L (>400 IU/L)	Pao <sub>2</sub> <60 mm Hg (omitted)
Serum aspartate aminotransferase level >250 IU/L (same)	Blood urea nitrogen level increase >5 mg/dL after intravenous fluid hydration (>2 mg/dL)
	Base deficit of >4 mmol/L (>6)

NOTE. The criteria for nongallstone (alcoholic) acute pancreatitis are listed first; the changes (if any) in the criteria for gallstone pancreatitis are in parentheses.

Adapted from Ranson et al.<sup>33,34</sup>

ration on pulse oximetry, white blood cell count, platelet count, hematocrit, blood urea nitrogen level, creatinine level, calcium level).

Patients who develop a poor outcome in acute pancreatitis typically have SIRS, characterized by tachycardia, tachypnea, hypocarbia, high or low core body temperature, and/or high or low peripheral white blood count, which an experienced clinician will recognize (Table 4).<sup>48</sup> A recent retrospective analysis of 759 patients admitted with acute pancreatitis noted much more frequent organ system failure and a mortality rate of 25% in those who presented with SIRS and had persistent SIRS during hospitalization.<sup>49</sup> In this same analysis, those with SIRS on admission who did not develop persistent SIRS had a mortality rate of only 8%, and those who did not present initially with SIRS had 0% mortality. In a sense, clinical judgment is also a multiple factor scoring system, although the factors scored are variable and not defined. In studies of the predictive ability of seasoned clinicians, the sensitivity of predicting severe disease at admission is 39%, with a specificity of 93%, a PPV of 66%, and an NPV of 82%.<sup>35</sup> At 48 hours, however, the accuracy of experienced clinical judgment is equivalent to APACHE II and other multiple factor scoring systems.

Several clinical predictors of poor outcome are worth mentioning directly. Age is a predictive factor for mortality in acute pancreatitis. Patients with more numerous and more severe comorbid illnesses are similarly more likely to experience morbidity and mortality during an episode of acute pancreatitis. Obesity is also a risk factor for severe disease. In a recent meta-analysis of 5 studies comprising 739 patients,<sup>50</sup> the odds ratio (OR) for severe acute pancreatitis was 2.9 (95% confidence interval [CI], 1.8–4.6), for systemic complications was 2.3 (95% CI, 1.4–3.8), for local complications was 3.8 (95% CI, 2.4–6.6), and for mortality was 2.1 (95% CI, 1.0–4.8). The observation that obesity is a risk factor for severe acute pancreatitis has led to the development of another variation of the APACHE II system, which includes up to 2 additional points for obesity. This system, the APACHE-O system, is superior in predicting outcome in some<sup>51</sup> but not all<sup>52</sup> studies.

These multiple factor scoring systems all have a substantial false-positive rate. Many patients with an APACHE II score >8 (or Ranson's score >3) do not develop complications or die. This is an unavoidable consequence of the fact that severe disease (organ failure,

**Table 4.** Features of SIRS

Heart rate	>90 beats/min
Temperature	>38°C or <36°C
Respiratory status	Respiratory rate >20 breaths/min or P <sub>a</sub> CO <sub>2</sub> <32 mm Hg
White blood cell count	>12,000 cells/μL or <4000 cells/μL or >10% band forms

**Table 5.** Balthazar CT Score

Grade	CT findings
A	Normal
B	Focal or diffuse enlargement of the pancreas, including irregularities of contour and inhomogeneous attenuation
C	Pancreatic gland abnormalities in grade B plus per pancreatic inflammation
D	Grade C plus a single fluid collection
E	Grade C plus 2 or more fluid collections and/or the presence of gas in or adjacent to the pancreas

Data from Balthazar et al<sup>53</sup> and Hirota et al.<sup>60</sup>

pancreatic necrosis, death) is not highly prevalent (about 15% of patients). In this situation, even tests of high specificity will have a low PPV.

Pancreatic necrosis has long been recognized as a major negative prognostic factor in acute pancreatitis and is included in the Atlanta criteria of severity. Balthazar et al produced a scoring system for acute pancreatitis based on the presence or absence of necrosis (Tables 5 and 6).<sup>16,17,53</sup> This system analyzes CT scans for evidence of both pancreatitis and necrosis and allows calculation of a CT severity index (Table 6). In a study of 88 patients,<sup>53</sup> the mortality of those with any degree of pancreatic necrosis was 23%, compared with 0% for those without necrosis. This study noted that the presence of more than 30% necrosis of the pancreas was most strongly associated with morbidity and mortality. Another study from the United Kingdom in 73 patients, of whom only 32 underwent CT, noted that necrosis predicted a severe outcome (death, major complication, or hospital stay longer than 20 days) with a sensitivity of 83% but a specificity of only 65% and noted no relationship between extent of necrosis and outcome.<sup>54</sup> A larger retrospective report in 268 patients<sup>55</sup> reported that a CT severity index of >5 correlated significantly with death ( $P = .0005$ ), prolonged hospital stay ( $P < .0001$ ), and need for necrosectomy ( $P < .0001$ ).

Extent of necrosis is one of the important factors of the CT severity index. Patients with a CT severity index >5 were 8 times more likely to die, 17 times more likely to have a prolonged hospital course, and 10 times more likely to undergo necrosectomy than their counterparts

**Table 6.** CT Severity Index

CT grade	Assigned score	Percent necrosis	Assigned score
A	0	None	0
B	1	<30	2
C	2	30–50	4
D	3	>50	6
E	4		

NOTE. CT grade based on Balthazar score (see Table 5) plus pancreatic necrosis with a maximum score of 10 points.

Data from Balthazar et al<sup>53</sup> and Hirota et al.<sup>60</sup>

with CT scores  $<5$ .<sup>55</sup> In a retrospective analysis of 99 patients with necrotizing pancreatitis admitted to a single referral center, more extensive necrosis was associated with increased need for intubation but no overall difference in organ failure, need for dialysis, or mortality.<sup>56</sup> A recent retrospective analysis from a referral center in India, however, described 276 patients (104 with necrotizing pancreatitis) and noted an association of increasing extent of necrosis and organ failure and mortality.<sup>57</sup> In this report, organ failure occurred in 5% of those with  $<30\%$  necrosis, compared with 24% of those with 30%–50% necrosis and 50% of those with  $>50\%$  necrosis. A number of studies have documented that only about half of patients with necrotizing pancreatitis develop organ failure.<sup>56,58,59</sup> The role of CT as a method to assess severity has been reviewed.<sup>17</sup>

In summary, the finding of necrosis on a CECT is generally associated with a worse prognosis, but only half of patients with necrosis develop organ failure. The mortality of patients with pancreatic necrosis is increased compared with those without. Data are conflicting on whether more extensive necrosis is associated with a worse clinical outcome, but the weight of the evidence suggests that more extensive necrosis is more likely to be associated with organ failure and poor outcome.

Gadolinium-enhanced MRI is reported to be equivalent to intravenous CECT for assessing the severity of acute pancreatitis, especially the presence or absence of necrosis.<sup>23–25,60,61</sup> The contrast agent (gadolinium) used for MRI does not carry the risk of renal impairment associated with iodinated contrast agents used for CT scanning. Experience with this technique is limited, and it can be difficult to perform MRI in critically ill individuals.

The judgment of prognosis should be based on all available evidence (clinical judgment, multiple factor scoring systems, CT, laboratory tests). The results of one recent study suggested that the Balthazar CT score is superior to Ranson's criteria and APACHE II and APACHE III in predicting necrosis but less accurate in predicting organ failure.<sup>45</sup> In one head-to-head comparison of Ranson's criteria, the Glasgow score, APACHE II, CT, and various serologic markers, APACHE II outperformed Ranson's criteria and the Glasgow criteria, whereas the combination of CT findings and the APACHE II results improved predictive ability over APACHE II alone.<sup>62</sup> In another recent report, CT scores outperformed APACHE II.<sup>63</sup> Other studies have found opposite results, with APACHE II outperforming CT.<sup>64</sup> These data alert clinicians that the wisest choice is to incorporate all available information into our estimate of prognosis.

The presence of organ failure is not truly a predictive system but rather a marker of severe disease. The Atlanta criteria define only 4 types of organ failure (shock, pulmonary insufficiency, renal failure, and gastrointestinal bleeding), although disseminated intravascular coagulation and metabolic abnormalities (severe hypocalcemia)

are mentioned in the original report. In the Atlanta criteria, organ failure is either present or absent and no differentiation is made between single and multiple organ failure or between transient and persistent organ failure. Isenmann et al<sup>65</sup> reported that a subgroup of patients with severe acute pancreatitis had a significantly higher mortality than expected. They described these patients as having early severe acute pancreatitis. They were more likely to develop intractable organ failure. In this report, early severe acute pancreatitis was characterized by the presence of extended pancreatic necrosis and a complicated clinical course. The mortality in this group was substantial (42% vs 14%,  $P = .0003$ , in a comparison of 47 patients with early severe acute pancreatitis and 111 without organ failure). In the retrospective analysis mentioned previously,<sup>56</sup> mortality was noted to be especially increased in those presenting with organ failure at admission (47% vs 8% in those without) or in those with multiple organ failure (48% vs 0% with single organ failure). Another study of 121 patients<sup>66</sup> noted that the presence of organ failure on admission carried an overall mortality rate of 21% (vs 3% in those without organ dysfunction). This mortality was restricted to the group that had both organ failure on admission and deteriorating organ failure over time. Those with organ failure on admission who did not have deteriorating organ failure had no mortality. An analysis of 290 patients with predicted severe pancreatitis who had participated in a randomized trial of a platelet-activating factor antagonist, later shown to be ineffective, reported a mortality rate of 35% and a complication rate of 77% in those with early and persistent organ failure, versus 15% and 29%, respectively, for those with early but not persistent organ failure.<sup>67</sup> Other studies have reached very similar conclusions.<sup>68</sup> The presence of early organ failure and persistent or deteriorating organ failure are therefore the best markers of a poor outcome and mortality. Planned revisions to the Atlanta criteria will include definitions of severity that incorporate not only the presence of organ failure but also its timing and persistence. Organ failure can be quantified by several systems, including the Atlanta definitions as well as scoring systems developed for use in the ICU such as the modified Marshall system<sup>69</sup> or the Sequential Organ Failure Assessment system.<sup>70</sup>

A variety of laboratory markers have been identified that might allow clinicians to identify patients with severe acute pancreatitis (Table 7). Data are limited for these markers, and they have not been incorporated into routine clinical use with the exception of hematocrit and C-reactive protein. Hemoconcentration (along with oliguria, tachycardia, hypotension, and azotemia) would be expected in patients with massive third-space loss from severe acute pancreatitis. Brown et al reported in a prospective cohort study that an admission hematocrit  $>44\%$  and a failure of this to decrease at 24 hours were good indicators of pancreatic necrosis and predictors of

**Table 7.** Potential Laboratory Markers of Severe Acute Pancreatitis

Trypsinogen activation peptide	Serum or urine
C-reactive protein	Serum
Polymorphonuclear leukocyte elastase	Serum
Interleukin-6	Serum
Interleukin-1 $\beta$	Serum
Tumor necrosis factor or soluble tumor necrosis factor receptors	Serum
Chemokines (eg, interleukin-8)	Serum
Platelet activating factor	Serum
Procalcitonin	Serum
Antithrombin III	Serum
Substance P	Serum

organ failure.<sup>71</sup> In this study, the NPV of hematocrit at 24 hours was 96% for necrotizing pancreatitis and 97% for organ failure. Patients who did not experience hemoconcentration were unlikely to develop pancreatic necrosis or organ failure. A number of other retrospective analyses, using a wide variety of definitions of hemoconcentration, reached differing conclusions. While some investigators noted reasonable accuracy for admission hematocrit, others have found hemoconcentration less useful in predicting outcome in acute pancreatitis<sup>72-74</sup> (Table 8). A high serum creatinine level (>2.0 mg/dL) and/or marked hyperglycemia (>250 mg/dL) on admission were also shown in one recent study to be predictive of mortality.<sup>75</sup> The level of serum amylase or lipase on admission is not a useful predictor of outcome.

C-reactive protein is widely used in Europe as a predictor of severe pancreatitis. C-reactive protein values at admission are not predictive of outcome,<sup>49</sup> but measurement at 48 hours has reasonable accuracy.<sup>76</sup> Most studies use a cutoff of 150 mg/L. In one systematic review of C-reactive protein,<sup>35</sup> the sensitivity at 48 hours for severe pancreatitis was 80% with a specificity of 76%, a PPV of 67%, and an NPV of 86%. These values are comparable (and in some studies superior) to the predictive value of Ranson's criteria or the Glasgow criteria and APACHE II

scores. C-reactive protein is not widely used in the United States for this purpose but deserves more widespread clinical application.

In summary, no highly sensitive and specific test or system exists that can accurately measure prognosis at admission. At the time of admission, clinical judgment should take into account clinical risk factors (age, comorbid conditions, obesity) as well as evidence of the presence or absence of SIRS, evidence of other worrisome features (delirium, coma), organ failure on admission, and routinely available laboratory abnormalities (hypoxia, azotemia, hemoconcentration). The use of the APACHE II scoring system at admission is a reasonable adjunct to clinical decision making. This approach has relatively good NPV (patients lacking any of these risk factors are exceedingly unlikely to have severe pancreatitis) but only modest PPV (many patients with some of these features will not develop severe acute pancreatitis). Nonetheless, these considerations are reasonable in determining whether patients should be managed in the ICU or intermediate care unit or whether a regular medical floor bed is adequate. A refined prediction of severity at 48 hours can be achieved by use of the APACHE II scoring system, C-reactive protein level, and/or ongoing clinical judgment. CT scans can provide additional prognostic information at 72 hours. By this time, of course, it may already be obvious that the patient has severe disease based on persistent SIRS or the development of single or multiple organ failure. The development of organ failure defines severe acute pancreatitis, but not all organ failure is equally morbid. Early (on admission) organ failure, persistent organ failure (beyond 48-72 hours), and multiple organ failure are particularly associated with morbidity and mortality.

### Determination of Etiology

The accurate determination of etiology allows a clinician to choose the most appropriate therapy for an individual patient. Advances in cross-sectional imaging

**Table 8.** Relationship of Hematocrit and Severity

Authors (reference), year	Study design	n	Definition of hemoconcentration	Sensitivity	Specificity
Baillargeon et al, <sup>73</sup> 1998	Case control	32 cases, 32 control	Hematocrit $\geq$ 47% and/or failure to decrease at 24 hours	34% at admission, 81% at 24 hours	91% at admission, 88% at 24 hours
Brown et al, <sup>71</sup> 2000	Cohort	53	Hematocrit $\geq$ 44% and/or failure to decrease at 24 hours	72% at admission, 94% at 24 hours	83% at admission, 69% at 24 hours
Lankisch et al, <sup>72</sup> 2001	Cohort	316	Hematocrit >43% (males), hematocrit >39.6% (females)	74% at admission (35% if use cutoff of hematocrit >47%)	45% at admission (87% if use cutoff of hematocrit >47%)
Remes-Troche et al, <sup>74</sup> 2005	Cohort	336	Hematocrit >44% (males), hematocrit >40% (females)	59% at admission	35% at admission

**Table 9.** Causes of Acute Pancreatitis

Biliary
Gallstones, microlithiasis, “biliary sludge”
Alcohol
Anatomic variants
Pancreas divisum, choledochal cyst, duodenal duplication, santorinicele, duodenal diverticula
Mechanical obstructions to flow of pancreatic juice
Ampullary: benign and malignant tumors, stricture or dysfunction of SOD
Ductal: stones, strictures, masses (including tumors), mucus (eg, in intraductal papillary mucinous neoplasms), parasites ( <i>Ascaris</i> )
Metabolic
Hypercalcemia, hypertriglyceridemia
Drugs
Toxins
Trauma
Blunt and penetrating, instrumentation (ERCP, pancreatic biopsy)
Ischemia
Hypotension, arteritis, embolic
Hypothermia
Infections
Viral (mumps, Coxsackie A, human immunodeficiency virus)
Bacterial/other: M tuberculosis, mycoplasma
Parasites ( <i>Ascaris</i> )
Venoms (spider, Gila monster)
Autoimmune
With or without associated autoimmune diseases (sicca syndrome, primary sclerosing cholangitis, autoimmune hepatitis, celiac disease)
Genetic (familial, sporadic)
Idiopathic

and molecular biology and genetics have greatly broadened the spectrum of possible etiologies, although perhaps 10%–15% of cases of acute pancreatitis remain unexplained (Table 9). The commonest cause of acute pancreatitis in most areas of the world is gallstones (including microlithiasis), accounting for at least 35%–40% of cases<sup>77,78</sup> and significantly more in some regions. Alcohol abuse is usually listed as the second commonest cause, despite the fact that acute pancreatitis rarely occurs in alcoholic patients without underlying changes of chronic pancreatitis already being established (ie, a single “binge” is unlikely to result in acute pancreatitis). Alcohol is responsible for about 30% of all cases of acute attacks in the United States.

The diagnosis of gallstone or biliary pancreatitis should be suspected based on patient demographics, abnormal liver chemistries at the time of an attack, and/or the results of abdominal ultrasonography demonstrating cholelithiasis or bile duct dilation. Gallstone pancreatitis is much more common in women and in more elderly individuals. If an attack of pancreatitis is associated with elevation of the serum alanine aminotransferase level to >3 times the upper limit of normal, there is a 95% likelihood that the source of the pancreatitis is biliary.<sup>14,15</sup> A number of studies have analyzed the predictive accuracy of liver chemistries for biliary pancreatitis and have proposed a variety of different cutoffs (eg, alanine

aminotransferase level >2 times the upper limit of normal, serum bilirubin level >2 mg/dL). In general, any significant abnormality of liver chemistries in a patient with acute pancreatitis should raise the possibility of a biliary source. Most patients with acute pancreatitis will undergo abdominal ultrasonography. If gallstones or a dilated bile duct are identified, gallstone pancreatitis is also quite likely. Gallstones may be missed on ultrasonography in some patients with gallstone pancreatitis (usually due to poor visualization from overlying gas); repeating ultrasonography after recovery is usually diagnostic in these patients. The most accurate method to identify cholelithiasis or choledocholithiasis in a patient with acute pancreatitis is endoscopic ultrasonography (EUS). Several recent reports document the accuracy of this technique but also note that the combination of clinical (age, sex), laboratory, and transabdominal ultrasound features remain quite accurate in identifying patients with acute biliary pancreatitis.<sup>79–83</sup>

There is no definitive method to test for alcohol as the cause of pancreatitis and no lower threshold of alcohol consumption below which alcohol cannot cause pancreatitis. Most patients, however, will have a history of prolonged and substantial use of alcohol or, rarely, a serious binge. The CAGE questions (Have you ever felt you should cut down on your drinking? Have people annoyed you by criticizing your drinking? Have you ever felt bad or guilty about your drinking? Have you ever had a drink first thing in the morning [eye opener] to steady your nerves or get rid of a hangover?) and discussions with family members are useful adjuncts for identifying alcohol abuse as a potential cause.

In patients without cholelithiasis, or who have already had their gallbladder removed, and who do not obviously drink alcohol, a number of less common causes can be considered. Anatomic abnormalities predisposing to acute pancreatitis include pancreas divisum, choledochal cysts (with or without anomalous pancreaticobiliary ductal union), duodenal duplication, ampullary adenomas and carcinomas, and other mechanical obstructions to the pancreatic duct, including stones, benign and malignant strictures, mucin (associated with mucin-secreting tumors), parasites, and sphincter of Oddi dysfunction (SOD). One cause, malignancy (typically ductal adenocarcinoma but occasionally neuroendocrine and other tumors), deserves particular mention. Episodes of pancreatitis may precede the development of overt malignancy in the pancreas by many months. Unexplained recurrent pancreatitis in middle age and beyond should raise the suspicion of underlying malignancy, which should be looked for carefully. Pancreas divisum is common in the population (7%–8% of white people, although it is rare in black and Asian people), but very few of these patients actually develop pancreatitis. SOD refers to a collection of syndromes associated with stenosis or spasm of the sphincter muscle controlling the flow of bile

**Table 10.** Association of Drugs With Acute Pancreatitis

<b>Definite association</b>	
Aminosalicylates (sulfasalazine, mesalamine)	Pentamidine Sulfonamide
L-asparaginase	Tetracycline
Azathioprine	Thiazides
Didanosine	Valproic acid
Estrogen	Vinca alkaloids
Furosemide	6-Mercaptopurine
<b>Probable association</b>	
Chlorthalidone	HMG-CoA reductase inhibitors
Cyclosporine	Metronidazole
Ethacrynic acid	Rifampin
FK-506	Steroids
<b>Possible association</b>	
Acetaminophen	
Amiodarone	
Atenolol	
Carbamazepine	
Chlorpromazine	
Cholestyramine	
Cisplatin	
Contrast media	
Danazol	
Diazoxide	
Diphenoxylate	
Ergotamine	

Adapted from Runzi and Layer.<sup>87</sup>

and pancreatic juice into the duodenum. There are classification systems for pancreatic SOD, ranging from type I (documented episodes of relapsing pancreatitis) to type III (“pancreatic-type” pain in the absence of documentation of relapsing attacks). The relative importance of SOD as a cause of unexplained relapsing pancreatitis is not known, and the effect of endoscopic therapy is not clearly defined.<sup>84–86</sup> The workup of SOD requires specialized manometry of the pancreatic duct sphincter at the time of endoscopic retrograde cholangiopancreatography (ERCP), which is available only in certain specialist (referral) centers.

Metabolic abnormalities predisposing to acute pancreatitis include hypercalcemia (almost always the result of hyperparathyroidism) and hypertriglyceridemia (typically with serum triglyceride levels >1000 mg/dL). It should be remembered that acute pancreatitis can cause elevations in triglyceride levels as well, but not to this high level. Idiosyncratic drug reactions are often blamed for acute pancreatitis, although the “culprit” drug is frequently found later to be an innocent bystander. More than 300 drugs have been associated with attacks of acute pancreatitis (Table 10).<sup>87,88</sup> Antimetabolites, such as azathioprine and 6-mercaptopurine, are particularly prone to cause acute pancreatitis, as are many of the drugs used in the treatment of acquired immunodeficiency syndrome (by direct toxicity or by inducing hypertriglyceridemia). Toxins, such as organophosphate pesticides, have been noted to cause acute pancreatitis through cholinergic hyperstimulation. Blunt or penetrat-

ing trauma may cause pancreatitis; included in this would be instrumentation of the gland, as in ERCP. Fortunately, post-ERCP pancreatitis is usually mild, but in 2%–3% of cases the illness is severe (associated with necrosis of the gland) and fatalities do occur. Ischemia of the pancreas associated with hypotension, arterial inflammation (arteritis, as in systemic lupus erythematosus), and systemic arterial embolism (eg, after cardiac catheterization) can cause acute pancreatitis, as can hypothermia (the effects typically being masked until the recovery phase). Infection with certain viruses, including mumps, Coxsackie A, and human immunodeficiency virus, can cause acute pancreatitis. Certain bacterial infections, including those caused by *M tuberculosis* and other mycobacteria, and mycoplasma, may also be culprits. The venoms of certain arachnids and reptiles (eg, brown recluse spider, some scorpions, and the Gila monster lizard) can be toxic to the pancreas, causing pancreatitis through cholinergic hyperstimulation.

Recently identified causes of otherwise unexplained acute pancreatitis include autoimmune pancreatitis and genetic forms of pancreatitis. It has been recognized that some patients with autoimmune disorders ranging from sicca syndrome to primary sclerosing cholangitis to autoimmune hepatitis may have an autoimmune process involving the pancreas as well. These patients may have elevated serum immunoglobulin G subclass 4 (IgG4) levels, a bulky pancreas on cross-sectional imaging, and abnormalities in the pancreatic duct on ERCP (typically long or multifocal strictures, usually without marked dilation of the pancreatic duct).<sup>89,90</sup> These patients rarely present with acute or subacute pancreatitis, more commonly presenting with chronic pancreatitis or a pancreatic mass, which can be mistaken for pancreatic carcinoma. Because there are some data to suggest that this disorder may regress or even be cured with corticosteroids, the diagnosis should be actively considered in acute pancreatitis of uncertain origin. Familial (or genetic) pancreatitis refers to an interesting group of conditions in which the predisposition to develop chronic (and occasionally acute) pancreatitis is genetically determined. Families with clustering of pancreatitis have been known to researchers for half a century, but the pivotal finding by Whitcomb et al<sup>91</sup> of a classic single-gene missense mutation affecting cationic trypsinogen and the subsequent identification of other mutations in this molecule in affected families has opened the door to a much wider understanding of genetic susceptibility to both acute and chronic pancreatitis. Patients with trypsinogen mutations ultimately develop chronic pancreatitis, which early in the clinical course may present as unexplained acute pancreatitis. These trypsinogen mutations are autosomal dominant, and the family history is usually suggestive of that type of inheritance.<sup>92</sup>

Patients who are mixed heterozygotes for a variety of mutations in the cystic fibrosis transmembrane conduc-

tance regulator (*CFTR*) gene may develop pancreatitis in the absence of classic sinopulmonary features of cystic fibrosis.<sup>93,94</sup> While most of these patients with *CFTR* mutations are evaluated for unexplained chronic pancreatitis, some will also develop acute flares and be considered to have acute pancreatitis. Mutations in *CFTR* might also set the stage for susceptibility to acute pancreatitis from a separate insult to the gland. As an example, a link appears to have been established between *CFTR* gene mutations and the occurrence of acute pancreatitis in patients with pancreas divisum.<sup>95</sup> Mutations in the serine protease inhibitor Kazal type 1 (*SPINK-1*) have also been described in patients with unexplained (mainly chronic but occasionally acute) pancreatitis.<sup>96,97</sup> A detailed discussion of the genetics of pancreatitis is beyond the scope of this review. While some of these mutations may be associated with acute pancreatitis, the primary presentation is chronic pancreatitis (or pancreatic malignancy). Many patients with these mutations may not even develop pancreatitis. Genetic screening for these mutations is not currently recommended in patients with unexplained acute pancreatitis for a number of reasons, including complexity, cost, and relatively low yield. However, it is likely that genetic screening may play an increasingly prominent role in the workup of idiopathic pancreatitis in the near future.

A detailed clinical history, simple laboratory tests, and imaging studies such as abdominal ultrasonography will reveal the likely cause of acute pancreatitis in many cases. These rather simple initial steps will identify the majority of patients with the 2 most common causes of acute pancreatitis: gallstones and alcohol. The history may also identify a history of hyperlipidemia, a drug exposure, iatrogenic events (eg, emboli after cardiac catheterization, post-ERCP pancreatitis), or associated autoimmune disorders (eg, sicca syndrome) that may provide important clues to etiology. Laboratory testing should include liver chemistries and serum calcium and triglyceride levels. Hypertriglyceridemia may be missed if the blood is drawn after the patient has been fasting for any prolonged period. In this situation, it is appropriate to repeat estimation of fasting triglyceride levels after recovery. Occasionally, patients with a fasting triglyceride level that is elevated but not to the level that typically causes pancreatitis will have a dramatically elevated postprandial triglyceride level. In patients with a suspicion of autoimmune pancreatitis, levels of antinuclear antibody and serum IgG4 should also be obtained, although elevation in IgG4 level is no longer considered pathognomonic for this condition.

When these more common potential etiologies are excluded by history, laboratory studies, and imaging tests, more rare or unusual conditions should be considered. In patients with an intact gallbladder, occult cholelithiasis or microlithiasis is the most likely etiology. Occult cholelithiasis (missed by transabdominal ultra-

sonography) is best detected by repeating the transabdominal ultrasonography or by EUS or magnetic resonance cholangiopancreatography (MRCP). The gold standard for diagnosis of microlithiasis is microscopic analysis of gallbladder bile, usually obtained by administering cholecystokinin and obtaining the darker "B" bile through an endoscope, tube, or catheter. There is no universally accepted method for analyzing bile and no universal criteria for what constitutes an abnormal test result.<sup>98</sup> There is some evidence that EUS can identify patients with microlithiasis, with a sensitivity of about 90%.<sup>80-83</sup> The finding of "sludge" in the gallbladder on EUS or transabdominal ultrasonography can be difficult to interpret because "sludge" may form with prolonged fasting (common in pancreatitis) and may represent the consequence rather than the cause of pancreatitis. Given the lack of a standardized method for diagnosing microlithiasis, empiric cholecystectomy may be considered in patients with gallbladder in situ and unexplained relapsing acute pancreatitis.<sup>84,99,100</sup> This is not an unreasonable approach in selected patients with gallbladder in situ who have recurrent attacks and in whom other common etiologies (alcohol, metabolic, structural) have been ruled out by history, screening laboratory tests, and imaging tests.

The consideration of malignancy as a potential etiology of unexplained acute pancreatitis would be appropriate in patients at risk (age older than 40 years) and/or patients with worrisome associated features (weight loss, new-onset diabetes mellitus). In such a patient, if not already done, cross-sectional imaging of the pancreas and pancreatic duct is appropriate. This could include a CT with pancreas protocol or MRI, often coupled with MRCP. Alternatively, EUS could be used in this situation to screen not only for malignancy but also to assess for ampullary masses, pancreatic ductal dilatation, signs of underlying chronic pancreatitis, and microlithiasis. EUS is particularly well suited to this situation. If EUS is not available, MRI and MRCP are preferred before considering ERCP.

If ERCP is ultimately performed, it should be done in a setting with appropriate expertise and technical support to evaluate and treat pancreas divisum, benign and malignant ductal strictures, ampullary lesions, and congenital abnormalities such as choledochocoele or anomalous pancreaticobiliary junction. If these etiologies are not identified, SOD manometry should be considered and ideally would be performed in the same setting. If performed, it is appropriate to measure pressures in both biliary and pancreatic sphincters because elevations in sphincter resting pressure may not always affect both segments of the sphincter. Sustained elevations of basal (over duodenal baseline) sphincter pressure >40 mm Hg are believed to be an indication for biliary and/or pancreatic sphincterotomy. The role and timing of ERCP in patients with unexplained pancreatitis and the importance of pan-

creas divisum and SOD are controversial.<sup>84–86,98–101</sup> ERCP is most appropriate in patients with recurrent or relapsing acute pancreatitis.<sup>100,101</sup> Typically, ERCP is not performed after a single episode of acute pancreatitis unless there is laboratory or imaging evidence of a bile duct stone. It is important for clinicians to remember that the majority of patients with a single episode of unexplained acute pancreatitis do not have a second attack.<sup>102,103</sup>

The rare case of acute pancreatitis (rather than chronic) associated with genetic disorders can only be elucidated by specific tests for the most common mutations (eg, in cationic trypsinogen, CFTR, SPINK-1). Unfortunately, at present there is no specific treatment for pancreatitis of genetic origin. It is a wise precaution to send patients with a suspected genetic basis for their pancreatitis to a genetics counselor before testing, because genetic screening has the potential to raise uncomfortable questions regarding paternity or maternity that the gastroenterologist is ill equipped to deal with.

## Management

The management of patients with acute pancreatitis should include closely monitored general supportive care, efforts to limit complications and appropriate treatment if complications occur, and prevention of recurrences.

### General Supportive Care

Supportive care includes appropriate triage, adequate fluid resuscitation, correction of electrolyte and metabolic imbalances, effective pain control, and provision of nutrition if a prolonged period of “nothing by mouth” is anticipated. Triage decisions on the use of an intermediate care unit or ICU are based on the presence of SIRS, organ failure, severe comorbid conditions, or other factors such as hemoconcentration or multiple factor scoring systems. These decisions will be influenced by the relative intensity of nursing support available in these units in individual hospitals. The presence of hypoxia, tachypnea, delirium, significant gastrointestinal bleeding, features of massive third-space loss (hypotension, tachycardia, azotemia, marked hemoconcentration), or evidence of SIRS would merit consideration of triage to an ICU environment.

Adequate early fluid resuscitation is crucial in appropriate management. Even in rather mild acute pancreatitis, fluid losses may be significant. In severe acute pancreatitis, fluid needs of 5 L or more daily are not uncommon. In animal models, adequate fluid resuscitation reduces morbidity and mortality.<sup>104,105</sup> Hemoconcentration, a marker of more substantial third-space losses, is associated in some studies with a higher likelihood of pancreatic necrosis and organ failure.<sup>71</sup> In one retrospective analysis, all patients who developed worsening hemoconcentration after 24 hours of hospital admission despite attempts at fluid resuscitation developed

necrotizing pancreatitis.<sup>106</sup> Hypotension or shock may occur not only as a consequence of massive fluid losses but also due to a decrease in peripheral and pulmonary vascular resistance and a compensatory increase in cardiac index, similar to the sepsis syndrome.<sup>107</sup> Finally, the ability of the pancreatic microcirculation to vasodilate in response to hypoperfusion is quite limited. Taken together, these observations support the role of vigorous fluid resuscitation. Crystalloid is preferred in most instances. Colloid may be considered in limited situations: packed red blood cells when the hematocrit falls below 25% and albumin if the serum albumin level drops to <2 g/dL. Adequate fluid resuscitation should produce a urine output of at least  $0.5 \text{ mL} \cdot \text{kg body wt}^{-1} \cdot \text{h}^{-1}$  in the absence of renal failure. Complications of fluid therapy include electrolyte disturbances and fluid overload. The latter is most concerning, especially in patients who have developed cardiovascular dysfunction or a pulmonary capillary leak syndrome (acute respiratory distress syndrome) as a consequence of acute pancreatitis. In this situation, the use of a central venous or pulmonary artery catheter may be helpful in gauging fluid needs.

Supplemental oxygen is needed in many patients. Hypoxia is quite common in acute pancreatitis due to splinting, atelectasis, pleural effusions, and the opening of intrapulmonary shunts.<sup>108</sup> The acute respiratory distress syndrome occurs in up to 20% of patients with severe acute pancreatitis. Patients with severe or moderately severe acute pancreatitis should be monitored by pulse oximetry for the first 48–72 hours. Persistent or progressive hypoxia will usually require admission to an ICU and possibly the use of mechanical ventilation. Pleural effusions do not usually require thoracentesis unless they are large and interfering with ventilation.

A number of electrolyte or other metabolic abnormalities can develop in the setting of acute pancreatitis.<sup>108</sup> Hypocalcemia is relatively common and is included on some of the prognostic multiple factor scoring systems as a marker of poor prognosis. Hypoalbuminemia is the most important factor causing low serum calcium levels, because most patients have normal levels of ionized calcium. Correction of hypocalcemia is usually not needed unless ionized levels of calcium are low or signs of neuromuscular instability develop (tetany, Chvostek’s sign, or Trousseau’s sign). Magnesium levels are also often low in this setting and may, in fact, explain some of the hypocalcemia. Hyperglycemia is also common and, like calcium, is included as a marker of poor prognosis in multiple factor scoring systems. Hyperglycemia can be due to parenteral nutritional therapy, inappropriately decreased insulin release, increased gluconeogenesis, and decreased glucose utilization. Insulin, at least on a temporary basis, is needed in most patients with severe acute pancreatitis and many with milder disease. Hyperglycemia substantially worsens neutrophil function<sup>109</sup> and may increase the risk of secondary pancreatic infections

(see following text), so careful monitoring of serum glucose levels and the use of sliding-scale insulin to keep blood sugar levels under good control are warranted. Hypertriglyceridemia is associated with acute pancreatitis, both as an etiology and as a consequence. Hypertriglyceridemia occurs in about 20% of patients with acute pancreatitis. Levels of serum triglycerides >1000 mg/dL are the cause, rather than the consequence, of acute pancreatitis. These patients usually have an underlying type IV or V hyperlipoproteinemia, often associated with diabetes mellitus.<sup>110</sup> Triglyceride levels usually drop promptly when the patient is prescribed nothing by mouth, but occasional patients may require plasmapheresis to reduce triglyceride levels (those with very severe hypertriglyceridemia or pregnant women with hypertriglyceridemic pancreatitis). Close control of blood glucose levels is also needed to facilitate control of serum triglyceride levels.

Adequate control of pain is important for appropriate management. Parenteral analgesics are usually needed. The use of patient-controlled analgesia is usually advantageous. A number of parenteral narcotics are used, including meperidine, morphine, hydromorphone, and others. In the past, morphine was avoided due to a concern that it might cause spasm of the SOD and thus worsen acute pancreatitis, although there is no evidence in humans that this is so.<sup>111</sup> Meperidine is not without side effects, including the accumulation of a neurotoxic metabolite (normeperidine) and a relatively short duration of action, and many hospitals have severely limited the availability of intravenous meperidine. Hydromorphone may thus be preferred.

The approach to nutrition support has undergone substantial changes in the past several years. Nutritional support should be considered when patients are unlikely to be able to eat for at least 7 days. Artificial feeding has no role or benefit in patients with mild acute pancreatitis who are expected to begin eating within 7 days. In the past, the use of total parenteral nutrition (TPN) was considered standard. TPN was believed to allow feeding without stimulating the pancreas and potentially worsening acute pancreatitis. TPN is associated with a number of complications, particularly hyperglycemia and catheter sepsis. Both complications may be related, at least in part, to overfeeding and excessive carbohydrate loads. The delivery of enteral elemental nutrition into the mid- or distal jejunum does not stimulate pancreatic secretion.<sup>112,113</sup> A number of trials have now been conducted comparing enteral with parenteral nutritional therapy in patients with acute pancreatitis. A meta-analysis of 6 randomized trials of TPN compared with enteral nutrition<sup>114</sup> delivered by a nasojejunal tube placed beyond the ligament of Treitz noted an overall reduction in infections in those receiving enteral nutrition (relative risk, 0.45; 95% CI, 0.26–0.78) and a reduction in the need for pancreatic surgery (relative risk, 0.48; 95% CI, 0.23–

0.99) but no reduction in other complications (organ failure) or mortality. All of these studies have also shown enteral nutrition to be less costly than TPN. The advantage in cost and improvement in at least some important outcomes has led to a general shift toward enteral nutrition in patients with acute pancreatitis. While most studies have incorporated nasojejunal feeding, some have used nasogastric or nasoduodenal feeding instead. The delivery of an elemental or semielemental supplement to the duodenum reduces pancreatic stimulation by about 50%, compared with the delivery of complex polymeric formulas.<sup>115</sup> The inflamed pancreas may also be less responsive to stimulation by nutrients in the duodenum than previously believed, but it is not completely insensitive to stimulation.<sup>116</sup> One recent small randomized trial compared nasojejunal with nasogastric feeding, utilizing a low-fat semielemental formula, in 50 patients with predicted severe acute pancreatitis and found no differences in morbidity or mortality.<sup>117</sup> A second even smaller study reached similar conclusions,<sup>118</sup> but another small study comparing nasogastric feeding with TPN noted increased pulmonary and total complications in the nasogastric group.<sup>119</sup> These studies are not definitive, and confirmatory studies in larger groups of patients are needed before acceptance of nasogastric or nasoduodenal feeding into widespread clinical practice.

In summary, there is accumulating evidence that nasojejunal tube feeding is less expensive and less morbid than TPN and is the preferred method of delivering nutrition in patients with severe acute pancreatitis. A few caveats are important. The presence of severe ileus may limit the tolerance of enteral feeding and TPN may be required. The tubes are somewhat difficult to place and may require endoscopy for placement. A number of techniques have been described, most using a guidewire with placement of the tube over a wire after removal of the endoscope. Techniques using small-caliber endoscopes transnasally and standard endoscopes transorally with a nasal transfer device to bring the wire out of the nose are equally effective. Maintaining the tube in position may be challenging, and placing a clip to anchor the tube to the jejunal wall may be necessary.

### *Therapies to Limit the Frequency or Severity of Complications*

There have been a wide variety of therapies proposed as a method to reduce complications. The goal of these therapies is to reduce complications of organ failure and secondary infections. These strategies have been largely ineffective, with a few notable exceptions.

**Efforts to “rest” the pancreas.** The presumption that limiting stimulation of pancreatic secretion improves outcome seems logical and has been part of management strategies for many years. The simplest method of limiting pancreatic secretion is prescribing nothing by mouth. There is actually no evidence that this manage-

ment strategy reduces organ failure or secondary infections, but patients with pancreatitis are rarely able to eat in any event due to nausea and pain. A number of strategies have been studied as methods to reduce pancreatic stimulation further, beyond that which might be accomplished by prescribing nothing by mouth. These include nasogastric suction, H<sub>2</sub>-receptor antagonists, proton pump inhibitors, atropine, 5-fluorouracil, somatostatin, and octreotide. The data supporting the use of these maneuvers and agents are not very convincing. Twelve small controlled trials comparing somatostatin with supportive treatment or placebo have been reported, of which 6 were randomized. A meta-analysis of these randomized trials<sup>120</sup> found no improvement in mild pancreatitis but a reduction in overall mortality in patients with severe pancreatitis (OR, 0.39; 95% CI, 0.18–0.86). A similar meta-analysis of 7 randomized trials of octreotide<sup>120</sup> found no effect on mild pancreatitis and no statistically significant reduction in overall mortality in severe pancreatitis (OR, 0.64; 95% CI, 0.38–1.09). If 3 additional controlled but nonrandomized studies using octreotide were included, the improvement in overall mortality reached statistical significance. Of note, the largest single randomized trial (by far) of octreotide in 302 patients with moderate to severe acute pancreatitis found absolutely no effect on mortality, organ failure, or secondary infections.<sup>121</sup> Somatostatin is not easily available in the United States, and the data on octreotide are controversial, so neither can currently be recommended as routine management for acute pancreatitis. Some of these other strategies may be useful in patients with acute pancreatitis, despite the fact that they have no effect on the outcome of acute pancreatitis. For example, a nasogastric tube may be beneficial for nausea and vomiting and an H<sub>2</sub>-receptor antagonist may help prevent stress ulceration, although neither has an impact on the outcome from the pancreatitis itself.

#### Efforts to reduce or remove activated proteases.

The role of activated proteases in producing organ failure is not clear. In the past, these proteases were believed to be central to the systemic complications of severe acute pancreatitis. More recent data suggest that a proinflammatory cytokine cascade is primarily at fault. Studies using aprotinin (a synthetic antiprotease), fresh frozen plasma (to provide natural antiproteases), and peritoneal lavage (to remove proteases) have been ineffective in human acute pancreatitis. More recently, the small-molecular-weight antiprotease gabexate mesilate has been studied. Meta-analyses<sup>120,122</sup> of 5 randomized studies noted no decrease in overall mortality (OR, 0.94; 95% CI, 0.55–1.62) but found a reduction in the overall complication rate (OR, 0.7; 95% CI, 0.56–0.88). Gabexate mesilate is not available in the United States.

**Efforts to reduce SIRS.** The release of proinflammatory cytokines and chemokines with a sepsis-like syndrome (SIRS) and multiorgan failure produce much of

the early morbidity and mortality of severe acute pancreatitis. One cytokine that was proposed as a central player in SIRS is platelet-activating factor. The drug lexipafant, an antagonist of platelet-activating factor, has been tested in several randomized trials. While initial studies were positive, a large randomized trial of more than 1500 patients noted no beneficial effect.<sup>46,123</sup>

**The removal of common bile duct stones.** This method of limiting complications is obviously only applicable to those with gallstone pancreatitis. It has been believed that by the time most patients with gallstone pancreatitis present to the hospital, or shortly thereafter, the offending common bile duct stone has usually already passed into the duodenum. A proportion of patients may have persistent common bile duct stones, either those that are too large to easily pass the ampulla or multiple common bile duct stones with repeated episodes of stone migration through the ampulla. This group of patients has been believed to be at increased risk for complications (organ failure) and associated cholangitis.<sup>124</sup> In this subgroup of patients, removal of common bile duct stones might reduce or prevent complications. This was first attempted by early surgery, but this was abandoned when randomized trials documented increased morbidity and mortality in the early surgery group. Subsequent studies have focused on ERCP and sphincterotomy. There are now 4 randomized trials of ERCP and sphincterotomy in these patients.<sup>125–128</sup> The earliest study randomized 121 patients to ERCP within 72 hours or conventional treatment.<sup>125</sup> Sphincterotomy was only performed if common bile duct stones were present. This study noted an overall reduction in complications in the group randomized to early ERCP, but this advantage was entirely accounted for by the reduction in complications in those patients who were predicted to have severe pancreatitis (based on a modified Glasgow score  $\geq 3$ ). There was no improvement in outcome in those with predicted mild pancreatitis. There was also no difference in mortality. There was no difference in the rates of cholangitis in the 2 groups, and if patients with associated cholangitis were excluded from the analysis, the reduction in complications was still present. A subsequent study<sup>126</sup> randomized 195 patients to early ERCP (within 24 hours). Of these, only 127 had gallstone pancreatitis. This study did not document any reduction in local or systemic complications of severe acute pancreatitis but did note a reduction in biliary sepsis in the early ERCP group. There was no difference in mortality. The third study<sup>127</sup> randomized 238 patients with acute biliary pancreatitis but without jaundice to early ERCP within 72 hours. This study was not able to demonstrate any reduction in complications (including cholangitis) or mortality from early ERCP. These 3 randomized trials have been subjected to several meta-analyses.<sup>129–131</sup> In the most recent Cochrane Database review,<sup>131</sup> early ERCP was calculated to reduce complica-

tions of acute biliary pancreatitis nearly in half (OR, 0.56; 95% CI, 0.38–0.83). This improvement in outcome is entirely accounted for by the group with predicted severe pancreatitis (OR, 0.27; 95% CI, 0.14–0.53); there was no reduction in complications in the group with predicted mild pancreatitis. The same analysis showed no reduction in overall mortality for early ERCP, although another meta-analysis did calculate a reduction in mortality in the subgroup with predicted severe pancreatitis.<sup>130</sup> The fourth and most recent randomized trial<sup>128</sup> has not been included in these meta-analyses. In this most recent trial, 103 patients with acute biliary pancreatitis who also had a dilated bile duct ( $\geq 8$  mm) on initial ultrasonography and a bilirubin level  $>1.2$  mg/dL were randomized to early ERCP within 72 hours of admission. Patients with cholangitis were excluded. Although bile duct stones were seen and removed in 72% of the group randomized to early ERCP, there was no difference in the primary outcomes of organ failure, mean CT severity index, local complications, overall morbidity, or mortality.

Taken together, these data and clinical experience provide important guidelines for ERCP in the management of acute biliary pancreatitis. ERCP should be urgently performed when acute cholangitis has complicated acute biliary pancreatitis (about 10% of patients). ERCP should also be performed when clinical or radiographic features suggest a persistent common bile duct stone (a dilated common bile duct or visible common bile duct stone, or jaundice or persistently abnormal liver chemistry values). In some centers, EUS is used to identify patients with acute biliary pancreatitis who have persistent bile duct stones and thus select patients for early ERCP.

Early ERCP may also be considered in the absence of these situations, when biliary pancreatitis is severe or is predicted to be severe (based on APACHE II, Ranson's criteria, or modified Glasgow criteria). Early ERCP in this situation (for severe or predicted severe pancreatitis in the absence of concomitant cholangitis or a high suspicion of a persistent common bile duct stone) is more controversial, and the data from randomized trials are not uniform in support of this practice. If early ERCP is performed, it should be undertaken within 48–72 hours of the onset of illness. In these randomized trials, sphincterotomy was not performed in the absence of stones in the common bile duct; it is not known if this strategy is justified. The decision whether to perform sphincterotomy if no stones are visualized in the common bile duct at the time of ERCP is individualized and may be influenced by the size of the cystic duct, the size of stones remaining within the gallbladder, the size of the common bile duct, and the expected wait until cholecystectomy.

Irrespective of these issues, cholecystectomy is indicated as soon as possible and in no case beyond 2–4 weeks after discharge to prevent relapses of acute pancreatitis. In patients who are not fit for surgery, endoscopic sphincterotomy alone provides acceptable protection

from subsequent attacks of acute biliary pancreatitis.<sup>132</sup> In 8 case series comprising 320 patients with gallstone pancreatitis or choledocholithiasis and gallbladder in situ managed by ERCP and sphincterotomy alone, only 3 (1%) developed recurrent biliary pancreatitis but 56 (17%) developed other biliary symptoms or complications (such as acute cholecystitis or biliary colic).<sup>132–139</sup> This rate of biliary symptoms and complications is high enough to warrant laparoscopic cholecystectomy if the patient is fit for surgery.

In patients with mild or resolved acute biliary pancreatitis who are scheduled for cholecystectomy, there is usually little need for preoperative ERCP because the risk of persistent common bile duct stones is low. There is no evidence that routine preoperative ERCP reduces complications, cost, or length of stay.<sup>140</sup> A randomized trial of routine preoperative ERCP compared with selective use of postoperative ERCP based on the results of intraoperative cholangiography noted shorter hospital stays and lower cost in the postoperative ERCP group.<sup>141</sup> This trial excluded patients with associated cholangitis; urgent ERCP is obviously required in these patients. In patients with a high likelihood of persistent common bile duct stones, preoperative ERCP is appropriate. In one analysis, preoperative ERCP was the most cost-effective approach when the prevalence of common bile duct stones reached  $>80\%$ .<sup>142</sup> In situations in which the prevalence of common bile duct stones was  $<80\%$ , laparoscopic common bile duct exploration or, if unavailable, postoperative ERCP were most cost effective. In patients in whom a preoperative question exists as to the presence of persistent common bile duct stones, preoperative EUS or MRCP is appropriate rather than proceeding directly to ERCP.<sup>143</sup>

### *Prophylactic Antibiotics*

Infection of pancreatic necrosis is the major cause of morbidity and mortality in acute pancreatitis after the first week of illness. The prevention of infection in patients with pancreatic necrosis has therefore been a sought-after clinical goal. Early trials of antibiotic prophylaxis used antibiotics that were later shown to have inadequate penetration into pancreatic necrosis. Several recent randomized trials have assessed the efficacy of antibiotic prophylaxis using agents with better tissue penetration.<sup>144–151</sup> These trials have used different patient selection criteria, different antibiotics, different outcome measures, and different durations of treatment. Only 2 of these studies are double blinded.<sup>150,151</sup> Several systematic reviews and meta-analyses have been performed on these studies, but the heterogeneity of the studies reduces the reliability of such analyses. The most recent Cochrane Database review<sup>152</sup> combined data from 4 studies (not including the 2 most recent studies that are double blind) and concluded that prophylactic antibiotics reduced mortality (OR, 0.32;  $P = .02$ ) and pan-

creatic sepsis (OR, 0.51;  $P = .04$ ). The combined data did not demonstrate a statistically significant reduction in extrapancreatic sepsis, need for surgery, or secondary fungal infections. Another recent systematic review included data from one of the more recent double-blind trials<sup>150</sup>; the raw data demonstrated a 13% absolute risk reduction in pancreatic sepsis and an 8% absolute risk reduction in mortality.<sup>153</sup> Another recent meta-analysis<sup>130</sup> of the 5 highest-quality and most comparable studies noted a reduction in sepsis and mortality but not in pancreatic sepsis. In a subgroup analysis, the group that received imipenem also had a reduction in pancreatic sepsis.<sup>130</sup> A recent analysis compared the methodological quality of these studies with the absolute risk reduction in pancreatic sepsis and noted that the highest-quality studies demonstrated the least effect of antibiotic prophylaxis.<sup>154</sup> Finally, a recent double-blind trial of antibiotic prophylaxis using meropenem, which is available for review but still in press, showed no effect of antibiotic prophylaxis.<sup>151</sup> The fact that the only 2 double-blind trials<sup>150,151</sup> show no benefit of prophylactic antibiotics is noteworthy. The variety of possible interpretations of these conflicting studies has led to a variety of opinions on the relative benefits and advisability of prophylactic antibiotics.

Not unexpectedly, most of the original studies had high rates of antibiotic use in the conservative treatment groups, which makes for confusing interpretation. In addition, broad-spectrum antibiotics are not benign and are associated with increased risk of resistant organisms and possibly fungal superinfection. These considerations have led to a variety of opinions on the use of prophylactic antibiotics, despite the number of positive meta-analyses. The most recent practice guidelines from the United Kingdom make no recommendation for prophylactic antibiotic therapy.<sup>155</sup> It is quite reasonable, based on current data, to utilize antibiotics on demand (for clinical features of infection) rather than prophylactically. Most experts agree that if antibiotic prophylaxis is considered, it should be restricted to patients who are at reasonable risk of developing infected pancreatic necrosis (a cutoff of at least 30% of the gland being necrotic on CECT is a reasonable one). The choice of antibiotic should be one with adequate penetration into the necrotic material, either imipenem-cilastatin, meropenem, or a combination of a quinolone and metronidazole. In the meta-analysis mentioned previously,<sup>130</sup> only the subgroup receiving imipenem had a decrease in pancreatic sepsis. One randomized trial comparing imipenem with pefloxacin noted that imipenem was superior to pefloxacin.<sup>156</sup> The large randomized blinded study using ciprofloxacin and metronidazole noted no benefit of these antibiotics compared with placebo.<sup>150</sup> These data suggest that imipenem may have advantages over quinolones. However, the recent negative trial using the related drug meropenem raises questions about this possi-

ble advantage. Prophylactic antibiotic therapy, once started, should continue for no more than 14 days. If infection does develop, either within the pancreas or elsewhere, antibiotics should be tailored to the infecting organism. Long-term use of broad-spectrum antibiotics is associated with the development of resistant organisms. There has also been concern over the emergence of fungal superinfection in these patients, although a meta-analysis of 4 trials that reported on fungal superinfection<sup>130</sup> noted no difference (4.9% rate of fungal superinfection in the antibiotic group vs 6.7% in the placebo groups).

### *Management of Complications*

**General complications.** The development of organ failure, circulatory instability, or severe metabolic derangements requires the coordinated care of a team of physicians and health care personnel, including surgeons, radiologists, gastroenterologists, and critical care specialists. The management of infected pancreatic necrosis may likewise require the services of a group of experienced clinicians. Referral of patients to a major specialist center is appropriate for such patients, depending on the particular expertise available at the referring institution.

**Pancreatic necrosis.** The development of necrosis per se is not an indication for any specific intervention. The natural history of necrosis is quite variable. It may produce symptoms, become infected, or, in some patients, remain asymptomatic. Over time, necrotic material will evolve from a composition that is mainly solid through a mixture of solid and thick viscous liquid to mainly viscous liquid with few solid components. During this evolution, which may take weeks or even months, there is a tendency for the necrotic material to become walled off by a surrounding capsule of granulation tissue, in much the same way a pseudocyst is walled off by granulation tissue. This evolution from mainly solid to mainly liquid composition allows progressively less invasive therapies to be applied. When the collection is mainly solid, debridement generally requires laparotomy. When the collection is mainly liquid, endoscopic, percutaneous, and minimally invasive surgical techniques can successfully deal with the collection. These collections, which had been termed "organized pancreatic necrosis," are now generally termed "walled-off pancreatic necrosis," a term that is meant to denote this circumscribed collection undergoing this change in composition and encapsulation. The presence of an area of walled-off pancreatic necrosis is not an indication, in and of itself, for any treatment but may require treatment for secondary infection or other symptoms (such as obstruction of a surrounding hollow viscus).

Identifying walled-off or organized pancreatic necrosis requires first identifying the presence of necrosis and second, assessing the characteristics of the material within the collection. Identifying the presence of necrosis

is best achieved by a CECT. Because these patients are often weeks or months into their illness, reviewing a series of previous CT scans with a radiologist can usually assist the clinician in this process. MRI and EUS are best at characterizing the contents of the collection, particularly at assessing the amount of residual solid necrotic material within the collection. Although CT is probably best at identifying the presence of necrosis, it is not accurate at identifying the amount of residual solid material within an area of necrosis. Many collections of walled-off necrosis appear to be bland liquid collections on CT scan, while in fact they contain large quantities of solid material. The more solid material in the collection, the more difficult it is to manage with less invasive or noninvasive techniques.

**Pancreatic infections.** *Infected necrosis.* The diagnosis of infected pancreatic necrosis is usually based on Gram stain and culture of material obtained from the necrotic area by fine-needle aspiration (FNA). The diagnosis should be suspected based on clinical features (worsening abdominal pain, fever, leukocytosis), usually 1–2 weeks after disease onset. In this clinical situation, it is appropriate to obtain a CECT to assess for the location of necrotic areas of pancreas. The finding of gas within the pancreas is highly suggestive, although not diagnostic, of infected necrosis. FNA of necrotic areas is safe and has a high sensitivity and specificity for detecting infection.<sup>157–159</sup> In general, sterile necrosis should be managed conservatively, whereas infected necrosis usually requires some definitive therapy. The decision to perform FNA and the subsequent management decision should always be undertaken in conjunction with the surgeon who is consulting on the case.

The standard approach to infected necrosis has been open surgical debridement. A number of different surgical approaches have been reported, including single-stage and multistage approaches and with a variety of drainage and closure techniques.<sup>130</sup> The technique of necrosectomy is relatively standardized with a variety of methods to control subsequent drainage, including marsupialization of the lesser sac, wide-closed pancreatic drainage, continuous lavage of the cavity, and planned repeat necrosectomy with delayed primary closure. Less invasive surgical approaches have also been described, using laparoscopic techniques and equipment along the track of existing percutaneous drains.<sup>160–162</sup>

The choice of surgical approach largely depends on local expertise and preferences. There has been an increasing trend to delay surgery as long as possible, even in the face of a positive result on FNA, if the clinical situation allows. This delay has the advantage of allowing necrotic material to demarcate and begin to liquefy, making complete initial necrosectomy more likely, and reducing the need for repeated debridement. The delay-until-liquefaction strategy also allows nonsurgical therapies to be considered. There are numerous reports of successful

radiologic<sup>163–166</sup> and endoscopic<sup>167–171</sup> treatment for sterile and infected pancreatic necrosis. The difficulty in achieving debridement of semisolid material through small-caliber tubes is substantial, and successful radiologic or endoscopic treatment requires multiple tubes and a committed patient and clinician. Minimally invasive surgery, and endoscopic and radiographic drainage, become much more straightforward as the necrosis softens and eventually liquefies. The consistency of the necrotic material can therefore play a large role in selecting therapeutic options. The process takes time, often a number of weeks, and it is a mistake to assume that a large collection of necrotic material is soft or liquefied based on the CT appearance alone. It can be difficult to define the internal character of such a collection, but MRI and EUS provide the most reliable information. The choice of therapy for infected (or rarely sterile) necrosis is largely driven by local expertise. There are even reports of successful medical therapy of infected necrosis,<sup>172,173</sup> although this would not be expected of a reliably effective therapy. Increasingly, however, patients with infected necrosis are being managed expectantly with intravenous antibiotics and definitive therapy is delayed (if the clinical situation allows it) to allow the necrosis to partially liquefy and become walled off and hence allow less invasive therapy.

**Pancreatic fluid collections and pseudocyst.** Collections of fluid in and around the pancreas are common in patients with moderate or severe acute pancreatitis. These amorphous fluid collections rarely require specific therapy. Approximately half of these fluid collections will resolve within 6 weeks, and up to 15% will persist as encapsulated pseudocysts.<sup>174,175</sup> Many pseudocysts can be managed conservatively, particularly if they are small (<6 cm) and asymptomatic. Pseudocysts may produce symptoms (generally abdominal pain), obstruct surrounding organs (duodenum, stomach, or bile duct), become infected, rupture, or bleed. These complications require therapy.

Surgical, radiologic, and endoscopic options are available for the management of large or symptomatic or complicated pseudocysts. The choice of approach depends on location, size, pancreatic ductal anatomy, and, most importantly, local expertise. It is worthwhile to state that endoscopic treatment, utilizing EUS guidance, is becoming much more common and in many institutions is the primary procedure for pseudocysts with amenable anatomy. Before choosing therapy, it is incumbent on the clinician to make sure the collection is actually a pseudocyst and not a cystic neoplasm. In addition, it is very important to have some idea as to the character of the contents of the collection. On occasion, a large area of necrotic pancreas may appear to be a pseudocyst on CT, and it may not be easily apparent that the collection contains solid and semisolid material. Placing a tube (percutaneous or endoscopic) into this type of collection

will not achieve drainage and will instead just convert an uninfected “necroma” into an infected one. If any doubt exists, an MRI or EUS can be helpful in gauging the consistency of the cystic collection.

A few pseudocyst complications deserve specific mention. Infected pseudocysts are generally easy to manage with any of the available techniques, because the contents are generally fluid and easily drained through even small-caliber tubes. Bleeding from a pseudocyst may occur from an associated visceral pseudoaneurysm. This bleeding may remain within the pseudocyst or may reach the gut through a spontaneous rupture with fistula or through the pancreatic duct (hemosuccus pancreaticus). These patients may present with gastrointestinal bleeding or an unexplained drop in hematocrit. Urgent upper endoscopy is indicated in patients with pancreatitis and gastrointestinal bleeding, and the absence of any definable explanation for bleeding should prompt an emergent CT scan. Evidence of bleeding into the pseudocyst is usually visible on CT and the pseudoaneurysm may also be evident, although angiography may be required to identify the actual pseudoaneurysm. The therapy should be emergent angiography with embolization, rather than any attempt to drain the cystic collection. Unexplained gastrointestinal bleeding in a patient with pancreatitis or a history of a pseudocyst warrants emergent CT to assess for pseudoaneurysm.

### *Surgery*

Surgery has no immediate role in patients with mild acute pancreatitis. Patients with sterile pancreatic necrosis should be managed conservatively. Surgery for sterile pancreatic necrosis is only rarely required, and then usually only when a large necrotic collection is causing persistent unremitting symptoms due to its size (eg, a large necrotic collection compressing the stomach and preventing oral intake). In this situation, it is often worthwhile to delay therapy until the collection is walled off and becomes more liquefied, which will allow less invasive therapies to be applied. The development of infected pancreatic necrosis is an indication for intervention, with surgery or an alternative technique as described previously depending on the characteristics of the collection. Early surgery (within the first 14 days) should be avoided because it is associated with increased mortality.

### *Prevention*

**Prevention of post-ERCP pancreatitis.** Pancreatitis occurring after ERCP provides a rare opportunity for therapies designed to prevent pancreatitis. The risk of post-ERCP pancreatitis is dependent on a number of patient, endoscopist, and procedural factors. In one large prospective study, a number of risk factors were identified by multivariate analysis; these include a history of post-ERCP pancreatitis, normal serum bilirubin level,

suspected SOD, female gender, moderate-to-difficult cannulation,  $\geq 1$  pancreatic duct contrast injection, pancreatic sphincterotomy, balloon dilation of the biliary sphincter, and the absence of chronic pancreatitis.<sup>176</sup> In this study, these risk factors were additive. ERCP for presumed SOD in a woman with a normal serum bilirubin level in whom there was a difficult cannulation (an all-too-common scenario) resulted in a post-ERCP pancreatitis risk of more than 40%. A second large prospective study also identified a number of risk factors in multivariate analysis.<sup>177</sup> In this study, risk factors included minor papilla sphincterotomy, suspected SOD, history of post-ERCP pancreatitis, age younger than 60 years,  $\geq 2$  contrast injections into the pancreatic duct, and trainee involvement in the procedure. It is worth noting the slight difference in the findings from these 2 studies, but the similarities are more substantial. These risk factors have been confirmed in several additional studies,<sup>178–181</sup> and a recent meta-analysis<sup>182</sup> of 15 studies comprising >10,000 patients identified 5 risk factors: suspected SOD, previous pancreatitis, female gender, precut sphincterotomy, and injection of contrast in the pancreatic duct. These studies provide clinicians with a mechanism to estimate the risk of post-ERCP pancreatitis in individual patients, which should be part of any discussion with the patient during the informed consent process. Performing ERCP to investigate unexplained abdominal pain in the absence of surrogate markers of biliary pathology, such as a dilated bile duct or abnormal liver chemistry values, is a risky business. The benefit of endoscopic therapy (ie, sphincterotomy) is limited and unpredictable in this type of patient. As Dr Peter Cotton, one of the pioneers of ERCP, has pointed out, those most at risk from ERCP are those who need it the least.<sup>183</sup>

The exact mechanism of post-ERCP pancreatitis is unknown, but risk factors for its development are known. Reducing the risk of post-ERCP pancreatitis is possible with the following approaches. First, avoid ERCP if possible. This is obvious, but clinicians should focus on using noninvasive and less invasive techniques to answer the same question (particularly high-quality multidetector CT, MRI, MRCP, and EUS). Second, do not perform ERCP without appropriate training and/or experience. Multiple retrospective and some prospective studies note that better trained and/or more experienced biliary endoscopists have fewer complications (including pancreatitis) and have more successful outcomes. The guidelines for ERCP training are now publicly promulgated by professional societies, such as the American Society for Gastrointestinal Endoscopy.<sup>184</sup> Because >90% of ERCPs are now therapeutic, the “bar” has been raised considerably in terms of the training and experience needed to be a safe and proficient ERCP endoscopist. Third, keep up to date on new therapies that reduce the risk of post-ERCP pancreatitis. Although pharmacologic therapies using drugs such as somatostatin and gaxetate

mesilate are of questionable benefit, other agents continue to be tried and may ultimately be shown to be effective.<sup>185-189</sup> The data on endoscopic techniques to reduce the risk of post-ERCP pancreatitis have now shown that stenting the pancreatic duct orifice can reduce the risk of post-ERCP pancreatitis.<sup>190</sup> In a meta-analysis of 5 randomized controlled trials,<sup>190</sup> the risk of pancreatitis after stenting was estimated to be one third the rate in the nonstented patients (5.8% vs 15.5%, respectively). The number needed to treat to prevent one episode of post-ERCP pancreatitis is 10. There are some caveats. It is not always possible to place a pancreatic stent. The risk of post-ERCP pancreatitis is very high when placement of a pancreatic duct stent is attempted but fails<sup>191</sup>; the rate of failure seems to be less with small-gauge (3F) stents placed over a 0.018"-diameter wire. Another advantage of the 3F gauge, single pigtail, unflanged, 6- to 8-cm-long pancreatic stents is that most migrate out into the bowel spontaneously within 72 hours or so, avoiding the need for a second endoscopy to remove them. There is also some evidence that smaller stents are less likely to cause damage to the pancreatic duct. In most situations, these stents should be removed 3-5 days after placement if they do not spontaneously migrate. Some endoscopists may be unfamiliar with these stents and the small-diameter wires over which they are placed. Still, in high-risk situations (as described previously), an attempt to place a stent in the pancreatic duct should be made (and documented).

**Prevention of other forms of pancreatitis.** In those patients with a definitive cause of pancreatitis, therapy directed at the cause is usually effective at preventing recurrences. Patients with gallstone pancreatitis are likely to experience a recurrence without definitive therapy, and cholecystectomy is indicated during the index hospitalization or shortly thereafter. Prolonged waits (more than 4-6 weeks) before definitive therapy are to be avoided because recurrent biliary pancreatitis is highly likely. In those who have already had cholecystectomy or in those too ill to tolerate surgery, endoscopic sphincterotomy provides reasonable protection for further attacks. Convincing those with alcoholic pancreatitis to stop drinking has unpredictable effects on further attacks but has many other benefits and hence is encouraged. Control of triglyceride levels can prevent additional attacks of hyperlipidemic pancreatitis, and control of hypercalcemia also reduces the risk of recurrent pancreatitis in those rare patients with pancreatitis due to hypercalcemia. Corticosteroids have a beneficial effect on the natural history of autoimmune pancreatitis. Endoscopic treatment of pancreatic duct strictures, SOD, or pancreas divisum may also be effective in reducing future attacks of pancreatitis.

In patients without a clear etiology (idiopathic acute pancreatitis), recurrences are infrequent. In one study, only one of 31 patients had a recurrence over 36 months

of follow-up.<sup>102</sup> In another analysis of 106 patients with idiopathic acute pancreatitis, the recurrence rate was 9% over at least 2 years of follow-up.<sup>103</sup> These data would suggest that extensive and invasive evaluations (such as ERCP) are not needed after a single episode of acute idiopathic pancreatitis. One exception to this rule might be in patients in whom pancreatic cancer is more likely (older than 40 years of age, smokers), and even in this group an evaluation using MRI, MRCP, or EUS is preferable to using ERCP initially.

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