

## CLINICAL PRACTICE

## Acute Pancreatitis

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**A 56-year-old woman presents with severe epigastric pain and vomiting of 14 hours' duration, symptoms that had developed shortly after dinner the previous night. She has no history of alcohol use, takes no medications, and has no family history of pancreatitis. On physical examination, she has a heart rate of 110 beats per minute and moderate epigastric abdominal tenderness without peritoneal signs. The white-cell count is 16,500 per cubic millimeter, and the hematocrit is 49 percent. The serum amylase level is 1450 IU per liter, the serum lipase level is 3200 IU per liter, the serum alanine aminotransferase level is 280 IU per liter, and the serum lactate dehydrogenase level is 860 IU per liter. Calcium, albumin, triglyceride, and electrolyte values are normal. How should the patient be further evaluated and treated?**

## THE CLINICAL PROBLEM

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Acute pancreatitis accounts for more than 220,000 hospital admissions in the United States each year.<sup>1</sup> The disease occurs at a similar frequency among various age groups, but the cause of the condition and the likelihood of death vary according to age, sex, race, body-mass index (the weight in kilograms divided by the square of the height in meters), and other factors.

The most important risk factors for pancreatitis in adults are gallstones and excessive alcohol use, although clinically detected pancreatitis never develops in most persons with these risk factors.<sup>2,3</sup> The incidence of gallstone pancreatitis is increased among white women over the age of 60 years<sup>4,5</sup> and is highest among patients with small gallstones (less than 5 mm in diameter) or microlithiasis.<sup>3,5</sup> Excessive alcohol use as a cause of pancreatitis is more common among men than women<sup>6</sup>; the association between alcohol consumption and acute pancreatitis is complex but appears to be dose-dependent. Other causes include metabolic aberrations (e.g., hypertriglyceridemia), duct obstruction (e.g., related to a tumor or pancreas divisum), medications (e.g., azathioprine, thiazides, and estrogens), and trauma. In children, the distribution of causes differs from that in adults, with systemic diseases and trauma particularly common.<sup>7</sup> About 20 percent of cases in adults remain idiopathic, although this classification is expected to become less common as factors of genetic predisposition and environmental susceptibility are elucidated.<sup>8</sup>

Overall, about 20 percent of patients with acute pancreatitis have a severe course, and 10 to 30 percent of those with severe acute pancreatitis die. Despite improvements in intensive care treatment during the past few decades, the rate of death has not significantly declined.<sup>9</sup>

The pathogenesis of acute pancreatitis relates to inappropriate activation of trypsinogen to trypsin (the key enzyme in the activation of pancreatic zymogens) and a lack of prompt elimination of active trypsin inside the pancreas.<sup>8</sup> Activation of diges-

tive enzymes causes pancreatic injury and results in an inflammatory response that is out of proportion to the response of other organs to a similar insult. The acute inflammatory response itself causes substantial tissue damage and may progress beyond the pancreas to a systemic inflammatory response syndrome, multiorgan failure, or death.

#### STRATEGIES AND EVIDENCE

##### DIAGNOSIS

The clinical diagnosis of acute pancreatitis is based on characteristic abdominal pain and nausea, combined with elevated serum levels of pancreatic enzymes. In gallstone pancreatitis, the pain is typically sudden, epigastric, and knife-like and may radiate to the back. In hereditary or metabolic cases or in those associated with alcohol abuse, the onset may be less abrupt and the pain poorly localized. Serum amylase levels that are more than three times the upper limit of normal, in the setting of typical abdominal pain, are almost always caused by acute pancreatitis. Lipase levels are also elevated and parallel the elevations in amylase levels. The levels of both enzymes remain elevated with ongoing pancreatic inflammation, with amylase levels typically returning to normal shortly before lipase levels in the resolution phase.

Tests that are more specific for acute pancreatitis but less widely available evaluate levels of trypsinogen activation peptide<sup>10</sup> and trypsinogen-2.<sup>11</sup> Abdominal imaging by computed tomography (CT), magnetic resonance imaging (MRI), or transabdominal ultrasonography is useful in confirming the diagnosis of pancreatitis or ruling out other intraabdominal conditions as the cause of pain or laboratory abnormalities. Such imaging may also identify the cause of pancreatitis or its associated complications.

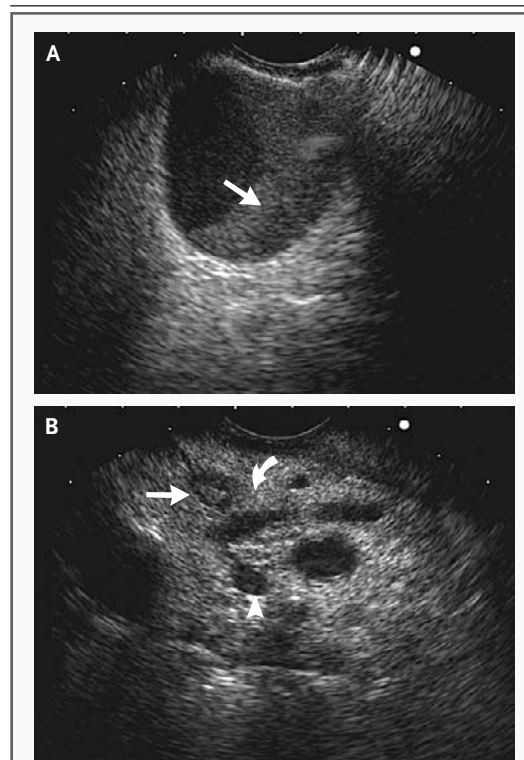
##### MANAGEMENT

Determination of the cause is important for guiding immediate management and preventing recurrence. An elevated alanine aminotransferase level in a patient without alcoholism who has pancreatitis is the single best laboratory predictor of biliary pancreatitis; a level of more than three times the upper limit of normal has a positive predictive value of 95 percent for gallstone pancreatitis.<sup>12</sup> However, the presence of normal alanine aminotransferase levels does not reliably rule out the di-

agnosis.<sup>4</sup> Laboratory testing may reveal hypertriglyceridemia or hypercalcemia as possible causes of pancreatitis, although pancreatitis may also cause mildly elevated triglyceride levels.

##### Imaging Studies

CT or MRI can identify gallstones or a tumor (an infrequent cause of pancreatitis), as well as local complications. MRI may also identify early duct disruption that is not seen on CT.<sup>13</sup> Transabdominal ultrasonography is more sensitive than either CT or MRI for identifying gallstones and sludge and for detecting bile-duct dilatation, but it is insensitive for detecting stones in the distal bile duct.<sup>4,5</sup> Endoscopic ultrasonography may be the most accurate test for diagnosing or ruling out biliary causes of acute pancreatitis (Fig. 1) and may guide the emergency use of endoscopic retrograde cholangiopancreatography (ERCP).<sup>14</sup>



**Figure 1. Endoscopic Ultrasonography of the Gallbladder and Common Bile Duct from the Duodenum.**

Microlithiasis (sludge) is shown within the gallbladder (Panel A, arrow) and within the common bile duct (Panel B, arrow). Also visible in Panel B are the head of the pancreas (curved arrow) and the pancreatic duct (arrowhead). (Images courtesy of Neeraj Kaushik, M.D.)

**Table 1. Scoring Methods for the Prediction of Severe Acute Pancreatitis.**

Criterion and Marker	Threshold Value	Severe Pancreatitis
<b>Atlanta criteria*</b>		
Ranson's score†	≥3	Indicated by any positive factor listed
APACHE II score‡	≥8	
Organ failure		
Shock	Blood pressure of <90 mm Hg	
Pulmonary insufficiency	Partial pressure of arterial oxygen of ≤60 mm Hg <sup>5</sup>	
Renal failure	Creatinine level of >177 μmol/liter (2 mg/dl) after hydration	
<b>Systemic complications</b>		
Disseminated intravascular coagulation	Platelet count of ≤100,000/mm <sup>3</sup> Fibrinogen level of <1 g/liter Fibrin-split products level of >80 μg/ml	
Metabolic disturbance	Calcium level of ≤7.5 mg/dl	
<b>Local complications</b>		
Pancreatic necrosis	Present	
Pancreatic abscess	Present	
Pancreatic pseudocyst	Present	
<b>Ranson's score†</b>		Indicated by a total score ≥3, with 1 point for each positive factor
<b>At presentation</b>		
Age	>55 yr	
Blood glucose level	>200 mg/dl (10 mmol/liter)	
White-cell count	>16,000/mm <sup>3</sup>	
Lactate dehydrogenase level	>350 IU/liter	
Alanine aminotransferase level	>250 IU/liter	
<b>Within 48 hr after presentation</b>		
Hematocrit	>10% decrease	
Serum calcium	<8 mg/dl (2 mmol/liter)	
Base deficit	>4 mEq/liter	
Blood urea nitrogen	>5 mg/dl (1.8 mmol/liter) increase	
Fluid sequestration	>6 liters	
Partial pressure of arterial oxygen§	<60 mm Hg	

**ERCP**

Persistent biliary obstruction worsens the outcome and increases the severity of acute pancreatitis and predisposes the patient to bacterial cholangitis. ERCP is used with endoscopic sphincterotomy to extract impacted gallstones and to drain infected bile in severe acute pancreatitis.<sup>15-18</sup> Although ERCP has risks, including bleeding after sphincterotomy and causing acute pancreatitis, complications are uncommon when the procedure is performed by experienced endoscopists. Three randomized trials involving a total of 511 patients with gallstone pancreatitis compared conservative manage-

ment with ERCP and endoscopic sphincterotomy within 24 to 72 hours after admission. The studies showed a significantly lower risk of pancreatitis-associated complications in the ERCP group (odds ratio, 0.27; 95 percent confidence interval, 0.14 to 0.53).<sup>16</sup>

**Hospitalization**

Patients who present with persistent or severe pain, vomiting, dehydration, or signs of impending severe acute pancreatitis (to be discussed later) should be hospitalized. Clinical trials have failed to show the efficacy of medications proposed to alter the

**Table 1. (Continued.)**

Criterion and Marker	Threshold Value	Severe Pancreatitis
<b>CT severity index¶</b>		Indicated by a total score of >6 (CT grade plus necrosis score)
CT grade		
Normal pancreas (grade A)	0 points	
Focal or diffuse enlargement (grade B)	1 point	
Intrinsic change; fat stranding (grade C)	2 points	
Single, ill-defined collection of fluid (grade D)	3 points	
Multiple collections of fluid or gas in or adjacent to pancreas (grade E)	4 points	
Necrosis score		
No pancreatic necrosis	0 points	
Necrosis of one third of pancreas	2 points	
Necrosis of one half of pancreas	4 points	
Necrosis of >one half of pancreas	6 points	
<b>APACHE II score‡</b>		Indicated by a score of ≥8
Initial values of 12 routine physiological measurements, age, and previous health status		

\* Data are from Bradley.<sup>21</sup> The Atlanta criteria were adopted in 1992 by the International Symposium on Acute Pancreatitis. The presence of any condition in the five main categories indicates severe acute pancreatitis.

† Data are from Ranson et al.<sup>22</sup> The original Ranson's score is based on 11 clinical signs (5 measured on admission and 6 in the 48 hours after admission), with a higher score indicating greater correlation with the incidence of systemic complications and the presence of pancreatic necrosis. The relationship between Ranson's score and the CT severity index<sup>23</sup> is given in Table 3.

‡ Data are from Knaus et al.<sup>24</sup> and Larvin and McMahon.<sup>25</sup> The Acute Physiology and Chronic Health Evaluation (APACHE II) score is based on initial values of 12 routine physiological measurements, age, and previous health status, with a score of 8 or more commonly used as the threshold for classification as severe pancreatitis.

§ The test was performed without the use of supplemental oxygen.

¶ The CT severity index<sup>23</sup> is a combination of the sum of the necrosis score and points assigned to five grades of findings on CT. The index ranges from 0 to 10, with higher scores indicating a greater severity of illness.

course of acute pancreatitis, including an inhibitor of platelet-activating factor (lexipafant<sup>19</sup>), somatostatin and its analogues, and protease inhibitors<sup>20</sup>; treatment is primarily supportive. Patients should receive nothing by mouth and receive intravenous pain medication and aggressive hydration to treat or prevent hemoconcentration (e.g., a bolus of fluids to achieve hemodynamic stability, followed by 250 to 500 ml of crystalloid solutions per hour in an average-sized patient without substantial kidney or heart disease). Fluid balance should be maintained and pulse oximetry should be considered, especially when narcotic analgesics are used.

#### *Predicting Severe Acute Pancreatitis*

The severity of acute pancreatitis is defined by the presence or absence of organ failure, local complications, or both<sup>21-25</sup> (Table 1). It is critical to identify patients who are at high risk for severe

disease, since they require close monitoring and possible intervention. Recognized markers of the risk of severe acute pancreatitis include specific laboratory values that measure the systemic inflammatory response (such as C-reactive protein), scoring systems that assess inflammation or organ failure (such as Ranson's score), and findings on imaging studies<sup>13,23</sup> (Table 2). The Acute Physiology and Chronic Health Evaluation score (based on initial values of 12 routine physiological measurements, age, and previous health status) is among the best predictors of severity on admission, whereas elevated C-reactive protein levels are equally useful when measured 24 to 48 hours after the onset of symptoms.<sup>27</sup> Severity scores are useful in predicting both complications and death (Table 3).

Other markers that are not included in standard scoring systems should also be considered. Obesity (a body-mass index of more than 30) is associated with an increase in the risk of a severe clinical

**Table 2. Value of Various Scoring Systems and Inflammatory Markers in the Prediction of Severe Acute Pancreatitis.\***

Scoring System	Sensitivity	Specificity	Positive Predictive Value percent	Negative Predictive Value	Accuracy
<b>On admission</b>					
APACHE II score†					
≥6	83–99	33–54	28–40	80–97	45–65
≥8	68–71	48–67	30–40	84–87	53–68
≥10	52–63	66–81	32–64	81–89	63–77
Interleukin-6 level >400 pg/ml	89	87	80	93	88
<b>At 24 hours</b>					
APACHE II score ≥8	63	73	38	88	71
C-reactive protein level >150 mg/dl	65	73	37	90	72
PMN elastase >300 μg/liter	93	99	97	98	98
Urinary TAP >35 nmol/liter	68	74	44	89	73
<b>At 48 hours</b>					
APACHE II score ≥8	56–78	52–64	30–33	85–88	58–63
Ranson's score ≥3	75–89	54–71	37–49	91–96	62–75
Modified Glasgow score ≥3‡	45–75	63–89	28–66	79–93	59–84
C-reactive protein level >150 mg/dl	65	73	37	90	72

\* PMN denotes polymorphonuclear leukocyte, and TAP trypsinogen activation peptide.

† Data are from Knaus et al.<sup>24</sup> and Larvin and McMahon.<sup>25</sup> The Acute Physiology and Chronic Health Evaluation (APACHE II) score is based on initial values of 12 routine physiological measurements, age, and previous health status, with a score of 8 or more commonly used as the threshold for the classification of severe pancreatitis.

‡ The Modified Glasgow score is similar to Ranson's score but can be completed on admission. The score ranges from 0 to 8, with scores of 3 or more indicating a greater severity of illness.<sup>26</sup> Data are from Papachristou and Whitcomb.<sup>27</sup>

course by a factor of 2 to 3.<sup>29</sup> A hematocrit above 44 percent is a clear risk factor for pancreatic necrosis,<sup>30</sup> although it is a poor predictor of the severity of disease. Preliminary evidence suggests that genetic factors, such as polymorphisms in the chemokine monocyte chemotactic protein 1 (MCP-1) gene,<sup>31</sup> may also predict severity, although such genetic testing is not currently used in practice.

Several clinical findings — including thirst, poor urine output, progressive tachycardia, tachypnea, hypoxemia, agitation, confusion, a rising hematocrit level, and a lack of improvement in symptoms within the first 48 hours — are warning signs of impending severe disease. If such symptoms develop, admission to an intensive care unit should be considered. Intensive care may also be warranted in patients at risk for rapid deterioration in their condition, including those over the age of 55 years,<sup>22</sup> those who need ongoing volume resuscitation or invasive monitoring of fluid status (e.g., central venous pressure monitoring), or

those with renal failure or respiratory compromise.<sup>15</sup>

#### *Pancreatic-Fluid Collections, Pseudocysts, and Necrosis*

Up to 57 percent of patients who are hospitalized with acute pancreatitis will have fluid collections, with 39 percent having two areas involved and 33 percent having three or more.<sup>32</sup> Fluid collections are initially ill defined,<sup>21</sup> evolve over time, and are usually managed conservatively. If the fluid collections continue to enlarge, cause pain, become infected (as suggested by the presence of unexplained fever, leukocytosis, or gas in the fluid collection), or compress adjacent organs, then medical, endoscopic, or surgical intervention may be needed.<sup>33,34</sup> Fluid collections with very high levels of pancreatic enzymes are usually associated with pancreatic-duct disruptions and may eventually form pseudocysts (usually over a period of several weeks), ascites, or pleural effusions.<sup>34</sup>



Asymptomatic pseudocysts can be managed conservatively, whereas symptomatic pseudocysts can often be drained endoscopically.<sup>35</sup> ERCP may help to define the anatomy of the pancreatic duct and identify any duct disruptions to guide further intervention.<sup>33,34</sup>

Pancreatic necrosis, occurring as diffuse or focal areas of nonviable pancreatic parenchyma,<sup>21</sup> is an important complication that can develop during the first few days of pancreatitis; the condition is associated with late complications and death if the necrotic tissue becomes infected. The development of necrosis is associated with pancreatic inflammation, hypovolemia, and hypotension from the shunting of blood from other organs, vascular spasm, and hemoconcentration.<sup>30</sup> Pancreatic necrosis can be demonstrated by a loss of tissue perfusion on contrast-enhanced CT.<sup>23</sup>

Infection of necrotic tissue is suspected when there is fever, leukocytosis, and a failure to improve or unexpected deterioration — usually after the first week of illness. Visualization of gas bubbles within the necrotic tissue on CT is evidence of infection. The diagnosis of infected necrosis is usually made by fine-needle aspiration of the necrotic area guided by either CT or ultrasonography, with Gram's staining and culture of the aspirate.<sup>36</sup>

#### *Lack of Improvement*

If the condition of a patient whose pancreatitis is predicted to be mild fails to improve within two or three days, then contrast-enhanced CT ("pancreas protocol") should be considered to identify fluid collections, pancreatic necrosis, or other complications that may require intervention. Antibiotic therapy and nutritional support also warrant consideration in patients whose condition fails to improve promptly or in whom complications develop.

#### *Use of Antibiotics*

The proper role of antibiotics in acute pancreatitis remains controversial. No antibiotics are indicated in mild cases. However, infectious complications are an important concern in severe cases, especially cases of pancreatic necrosis. A potential role for prophylactic antibiotics in severe pancreatitis was initially given support by a randomized trial demonstrating that the administration of imipenem reduced infectious complications, including central-line sepsis, pulmonary infection, urinary tract infection, and infected pancreatic necrosis.<sup>37</sup> Subsequent trials yielded mixed, but gen-

**Table 3. Relationship between Severity Scores and Outcomes in Acute Pancreatitis.\***

Index	Score			
	0–2	3–4	5–6	7–8
<i>percent of patients</i>				
Intensive care for >7 days and survival	1	24	53	NA
Death	3	16	40	100
Either intensive care for >7 days or death	4	40	93	100
<b>CT severity index</b>	0–3	4–6	7–10	NA
Complications	8	35	92	NA
Death	3	6	17	NA

\* Data are from Balthazar et al.<sup>23</sup> and Ranson.<sup>28</sup> NA denotes not applicable.

erally confirmatory, results.<sup>38</sup> However, a recent randomized trial failed to demonstrate differences in outcome among patients treated with ciprofloxacin plus metronidazole, as compared with placebo, leading some experts to recommend against the routine use of prophylactic antibiotics.<sup>39</sup> Some centers use antifungal therapy as well as antibacterial therapy, but this practice has not been validated by randomized trials.

#### *Nutritional Support*

Ensuring adequate nutrition is important in patients with severe or complicated pancreatitis, but the optimal means of doing so remains controversial.<sup>40</sup> Two small trials involving a total of 70 patients showed a nonsignificant reduction in adverse outcomes with enteral feeding through nasoenteric feeding tubes, as compared with total parenteral nutrition.<sup>41</sup> More recent meta-analyses of six randomized trials involving a total of 263 patients demonstrated improved outcomes with enteral nutrition,<sup>42,43</sup> including decreased rates of infection<sup>42,44</sup> and surgical intervention,<sup>42</sup> a reduced length of hospital stay,<sup>42</sup> and reduced costs (20 percent of the costs associated with total parenteral nutrition).<sup>43</sup> Enteral feeding is usually well tolerated in patients with ileus.<sup>40</sup> However, total parenteral nutrition may be necessary for patients who cannot obtain sufficient calories through enteral nutrition or in whom enteral access cannot be maintained.<sup>45</sup>

#### *Surgery*

Surgical intervention is indicated in patients with infected pancreatic necrosis. In most cases, the di-

agnosis is confirmed by fine-needle aspiration before surgical intervention, but because false negative results can occur (reported sensitivity, 88 percent),<sup>46</sup> surgery also warrants consideration when there is a high index of suspicion of infected necrosis even if infection is not documented.

Surgery within the first few days after the onset of severe acute pancreatitis is associated with rates of death up to 65 percent.<sup>47</sup> Furthermore, there is no clear demarcation between viable and nonviable tissue early in the course of acute pancreatitis.<sup>47</sup> Observational data support delaying surgical débridement of necrotic tissue for at least two weeks if possible while the patient's medical condition is optimized and viable pancreatic tissue becomes evident.<sup>47</sup> This approach appears to improve survival and maximize organ preservation.<sup>47</sup>

#### *Discharge Planning*

Whenever possible, the cause of pancreatitis should be determined and plans to prevent recurrence should be devised before the patient is discharged from the hospital. In patients with acute pancreatitis caused by gallstones, cholecystectomy should be considered before discharge in those with mild cases or within a few months in those with more severe or complicated cases to allow inflammatory processes or fluid collections to organize or resolve.<sup>47</sup> ERCP with sphincterotomy is an alternative in patients who are not surgical candidates or in whom surgery must be delayed.<sup>47</sup> If the cause is hypertriglyceridemia, then dietary measures, cessation of alcohol intake, weight reduction, and possibly, treatment with the administration of gemfibrozil or fenofibrate should be initiated.<sup>48</sup> The identification of hypercalcemia requires attention to the underlying cause, such as hyperparathyroidism or cancer. Medications associated with acute pancreatitis should be discontinued.<sup>49</sup> Recurrent pancreatitis — in the absence of biliary disease, alcoholism, and toxic or metabolic causes — suggests other causes, such as strictures, pancreas divisum, duct-obstructing masses, autoimmune pancreatitis, and genetic susceptibility.<sup>50</sup> Systematic approaches to idiopathic and recurrent acute pancreatitis have been reviewed elsewhere.<sup>50–52</sup>

Patients can be discharged when their pain is controlled with oral analgesics and they are able to eat and drink. Oral feeding can be started when abdominal tenderness diminishes and the patient becomes hungry. Clinical experience provides support for a recommendation that patients eat small,

low-fat meals of carbohydrates and proteins, with a gradual increase in quantity over a period of three to six days as tolerated.<sup>40</sup> Patients who are unable to eat because of persistent pain or gastric compression from a pseudocyst have been successfully treated as outpatients with nasoenteric feeding tubes, surgical jejunal tubes, or total parenteral nutrition.

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#### AREAS OF UNCERTAINTY

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Data from randomized trials are needed to identify ways to improve the management of acute pancreatitis, including the optimization of nutritional support and the prevention and treatment of infections and other complications.

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#### GUIDELINES

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The prophylactic use of antibiotics in patients with pancreatic necrosis is supported by the guidelines of the International Association of Pancreatology for the surgical management of acute pancreatitis<sup>47</sup> and the Japanese Society of Abdominal Emergency Medicine<sup>53</sup> but is discouraged by an expert panel of the American Thoracic Society and other organizations.<sup>15</sup> No consensus was reached by the United Kingdom Working Party on Acute Pancreatitis.<sup>17</sup> The last three organizations<sup>15,17,53</sup> favor the use of enteral nutrition over total parenteral nutrition in patients with severe acute pancreatitis whenever possible. Early intervention for gallstone pancreatitis with bile-duct obstruction with the use of ERCP with endoscopic sphincterotomy is consistently recommended.

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#### SUMMARY AND RECOMMENDATIONS

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In a patient presenting with acute pancreatitis, such as the woman in the vignette, immediate considerations include assessment of the severity and cause of the condition. The patient in the vignette has a Ranson's score that indicates a high risk of severe disease on the basis of her age, white-cell count, and levels of lactate dehydrogenase and alanine aminotransferase. She should be admitted to the hospital, receive aggressive hydration, and be closely monitored. Given her sex, age, absence of alcohol intake, and alanine aminotransferase levels, gallstones are the likely cause, and transabdominal or endoscopic ultrasonography should be performed to look for stones or sludge in the gall-

bladder. If the findings on imaging or the clinical presentation provide support for a biliary cause, consultation or transfer to a facility with an experienced therapeutic endoscopist is warranted, since emergency treatment with ERCP is useful in such patients. Nasoenteric feedings are recommended for most patients with severe pancreatitis; among patients whose condition is stable, such feedings should be started within two to three days after presentation. Data and clinical guidelines conflict with respect to whether antibiotics are indicated in severe acute pancreatitis. Pending more data to inform this decision, the use of antibiotics

should be reserved for patients with necrosis of more than 30 percent of the pancreas, since small areas of necrosis seldom become infected; the use of imipenem was associated with the prevention of infectious complications in two randomized trials.<sup>37,54</sup>

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