# Acute Pancreatitis

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THE INCIDENCE OF ACUTE PANCREATITIS IS INCREASING IN THE UNITED States, and the disorder is now one of the most common reasons for hospitalization with a gastrointestinal condition. In this review, we consider recent changes in the management of acute pancreatitis, as well as common misunderstandings and areas of ongoing controversy.

## CAUSES OF ACUTE PANCREATITIS

Table 1 lists the causes of acute pancreatitis. Gallstones are the most common cause.[1,2] Migrating gallstones cause transient obstruction of the pancreatic duct, a mechanism shared by other recognized causes (e.g., endoscopic retrograde cholangiopancreatography [ERCP]), as well as purported causes (i.e., pancreas divisum and sphincter of Oddi dysfunction). A recent trial failed to show that sphincter of Oddi dysfunction contributed to post-cholecystectomy biliary pain,[3] and there are no convincing data from controlled trials that either pancreatic sphincter of Oddi dysfunction or pancreas divisum plays a role in acute pancreatitis.[4-6]

Alcohol is the second most common cause of acute pancreatitis. Prolonged alcohol use (four to five drinks daily over a period of more than 5 years) is required for alcohol-associated pancreatitis[7]; the overall lifetime risk of pancreatitis among heavy drinkers is 2 to 5%. In most cases, chronic pancreatitis has already developed and the acute clinical presentation represents a flare superimposed on chronic pancreatitis. The risk is higher for men than for women, perhaps reflecting differences in alcohol intake or genetic background.[8] The mechanisms by which alcohol causes acute (or chronic) pancreatitis are complex and include both direct toxicity and immunologic mechanisms.[9] The type of alcohol ingested does not affect risk, and binge drinking in the absence of long-term, heavy alcohol use does not appear to precipitate acute pancreatitis.[10]

Drugs appear to cause less than 5% of all cases of acute pancreatitis, although hundreds of drugs have been implicated.[11] The drugs most strongly associated with the disorder are azathioprine, 6-mercaptopurine, didanosine, valproic acid, angiotensin-converting–enzyme inhibitors, and mesalamine. Pancreatitis caused by drugs is usually mild. Recent data do not support a role for glucagon-like peptide 1 mimetics in causing pancreatitis.[12] It is common for patients to be taking one of the many drugs associated with pancreatitis when they are admitted to the hospital with acute pancreatitis,[13] but it is exceedingly difficult to determine whether the drug is responsible.

Mutations and polymorphisms in a number of genes are associated with acute (and chronic) pancreatitis, including mutations in the genes encoding cationic trypsinogen (*PRSS1*), serine protease inhibitor Kazal type 1 (*SPINK1*), cystic fibrosis transmembrane conductance regulator (*CFTR*), chymotrypsin C, calcium-sensing receptor, and claudin-2.[14] These mutations may serve as cofactors, interacting with

**Table 1. Causes of Acute Pancreatitis.***

| Cause | Approximate Frequency | Diagnostic Clues | Comments |
|---|---|---|---|
| Gallstones | 40% | Gallbladder stones or sludge, abnormal liver-enzyme levels | Endoscopic ultrasonography can reveal very small gallbladder or duct stones. |
| Alcohol | 30% | Acute flares superimposed on underlying chronic pancreatitis | Diagnosis rests on history, obtained with CAGE questions.† |
| Hypertriglyceridemia | 2–5% | Fasting triglycerides >1000 mg/dl (11.3 mmol per liter) | |
| Genetic causes | Not known | Recurrent acute pancreatitis and chronic pancreatitis | |
| Drugs | <5% | Other evidence of drug allergy (e.g., rash) only in rare cases | The condition is idiosyncratic and usually mild. |
| Autoimmune cause | <1% | Type 1: obstructive jaundice, elevated serum IgG4 levels, response to glucocorticoids; type 2: possible presentation as acute pancreatitis; occurrence in younger patients; no IgG4 elevation; response to glucocorticoids | Type 1 is a systemic disease affecting the pancreas, salivary glands, and kidneys; in type 2, only the pancreas is affected. |
| ERCP | 5–10% (among patients undergoing ERCP) | | The symptoms can be reduced with rectal NSAIDS (diclofenac or indomethacin) or temporary placement of a stent in the pancreatic duct. |
| Trauma | <1% | Blunt or penetrating trauma, particularly in midbody of pancreas as it crosses spine | |
| Infection | <1% | Viruses: CMV, mumps, and EBV most common; parasites: ascaris and clonorchis | |
| Surgical complication | 5–10% (among patients undergoing cardiopulmonary bypass) | | The condition is probably due to pancreatic ischemia; pancreatitis may be severe. |
| Obstruction | Rare | Celiac disease and Crohn's disease, pancreas divisum (controversial), and sphincter of Oddi dysfunction (very controversial) | On rare occasions, malignant pancreatic duct or ampullary obstruction is seen. |
| Associated conditions | Common | Diabetes, obesity, and smoking | |

* CMV denotes cytomegalovirus, EBV Epstein–Barr virus, ERCP endoscopic retrograde cholangiopancreatography, and NSAIDs nonsteroidal antiinflammatory drugs.
† CAGE is an acronym for the following 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 to steady your nerves or to get rid of a hangover (eye opener)?

other causes; for example, claudin-2 mutations work synergistically with alcohol.[8,14]

The cause of acute pancreatitis often cannot be established, and the proportion of persons who are considered to have idiopathic acute pancreatitis increases with age. A number of potential factors might contribute to unexplained pancreatitis, including unidentified genetic polymorphisms, exposure to smoking and other environmental toxins,[15] and effects of coexisting diseases that are commonly associated with acute pancreatitis (e.g., obesity and diabetes). Morbid obesity is a risk factor for acute pancreatitis[2,16] and for severe acute pancreatitis.[17] Type 2 diabetes increases the risk of acute pancreatitis by a factor of 2 or 3.[2] Both obesity and diabetes are also risk factors for chronic pancreatitis and pancreatic cancer.[18]

## EPIDEMIOLOGY

Acute pancreatitis in the United States accounts for health care costs of $2.5 billion[19] and for 275,000 admissions each year. Admissions have increased by at least 20% over the past 10 years. Studies worldwide[20-22] have shown a rising but variable incidence of acute pancreatitis, including large increases in incidence in pediatric populations.[23] This increased risk of pancreatitis tracks with the worldwide obesity epidemic and increasing rates of gallstones. Approximately 80% of patients admitted with acute pancreatitis have mild, self-limited disease and are discharged within several days. Mortality associated with acute pancreatitis has decreased over time,[2] and the overall mortality is now approximately 2%. Death is more likely in certain subgroups of patients, including the elderly, those with more numerous and more severe coexisting conditions (particularly obesity),[16,17] those in whom hospital-acquired infections develop,[24] and those with severe episodes of acute pancreatitis (characterized by persistent failure of one or more organ systems or infected pancreatic necrosis).

## DIAGNOSIS AND CLASSIFICATION

Accurate diagnosis of acute pancreatitis requires at least two of the following three diagnostic features[25]: abdominal pain consistent with acute pancreatitis, serum lipase or amylase levels that are at least 3 times the upper limit of the normal range, and findings of acute pancreatitis on cross-sectional imaging (computed tomography [CT] or magnetic resonance imaging). Patients with vague abdominal symptoms and a minimally increased serum amylase or lipase level should not receive a diagnosis of acute (or chronic) pancreatitis. Cross-sectional imaging is invaluable in confirming an initial diagnostic impression, in assessing patients for other conditions that might mimic acute pancreatitis, and in evaluating patients with atypical symptoms or small elevations in serum pancreatic enzyme levels.

According to a recent international consensus (see the Supplementary Appendix, available with the full text of this article at NEJM.org), the classifications of moderately severe pancreatitis and severe pancreatitis are defined by the presence of complications that are systemic, local, or both. Systemic complications include failure of an organ system (respiratory, cardiovascular, or renal) and exacerbation of a preexisting disorder (e.g., chronic obstructive pulmonary disease, heart failure, or chronic liver disease). Local complications comprise peripancreatic fluid collections or pseudocysts and pancreatic or peripancreatic necrosis, whether sterile or infected.[25] In this classification system, persistent failure of an organ system (i.e., lasting more than 48 hours) is the prime determinant of a poor outcome. The overall mortality is approximately 2%, but it approaches 30% among patients with persistent failure of an organ system. According to another classification system, the presence of both persistent organ failure and infected pancreatic necrosis ("critical" pancreatitis) is associated with the highest mortality (see the Supplementary Appendix).[26]

By providing standardized definitions and descriptions of severity, as well as radiographic features, these classification systems for acute pancreatitis have value in clinical research. However, they do not provide methods for predicting severity.

## PREDICTION OF SEVERITY

Knowing which patient will have severe pancreatitis could allow earlier triage to an intermediate care or intensive care unit and earlier initiation of effective therapy. Prediction of severity has been accomplished through careful observation by an experienced clinician, with symptoms,

signs, and the results of routine laboratory and radiographic testing taken into account. This process largely allows the identification of severe pancreatitis as it develops. A host of predictors, including clinical and laboratory markers and various scoring systems, have been developed to improve clinical judgment.

Clinical factors that increase the risk of complications or death among patients with acute pancreatitis include advanced age (≥60 years), numerous and severe coexisting conditions (a score of ≥2 on the Charlson comorbidity index [a weighted sum of diseases according to the codes of the International Classification of Diseases, 10th revision, with higher scores indicating a greater disease burden]), obesity (a body-mass index of >30 [calculated as the weight in kilograms divided by the square of the height in meters]), and long-term, heavy alcohol use.[2] A variety of laboratory measures have also been studied, primarily measures of intravascular volume depletion due to third-space losses (i.e., the leakage of fluid from the intravascular spaces and into the interstitial spaces), such as hemoconcentration and azotemia, or markers of inflammation (e.g., elevated levels of C-reactive protein and interleukins 6, 8, and 10). Several of these measures have reasonable predictive value for severe acute pancreatitis. The most useful predictors are elevated blood urea nitrogen and creatinine levels and an elevated hematocrit, particularly if they do not return to the normal range with fluid resuscitation.[27,28] The degree of elevation of the serum amylase or lipase level has no prognostic value.

A number of predictive systems use CT findings, but CT evidence of severe acute pancreatitis lags behind clinical findings, and an early CT study can underestimate the severity of the disorder. Several scoring systems have been developed to incorporate clinical, radiographic, and laboratory findings in various combinations: Acute Physiology and Chronic Health Evaluation II (APACHE II), APACHE combined with scoring for obesity (APACHE-O), the Glasgow scoring system, the Harmless Acute Pancreatitis Score (HAPS), PANC 3, the Japanese Severity Score (JSS), Pancreatitis Outcome Prediction (POP), and the Bedside Index for Severity in Acute Pancreatitis (BISAP).[29] These scoring systems all have a high false positive rate (i.e., in many patients with high scores, severe pancreatitis does not

develop), which is an unavoidable consequence of the fact that in most patients, severe disease does not develop. The scoring systems are complex and cumbersome and not routinely used.
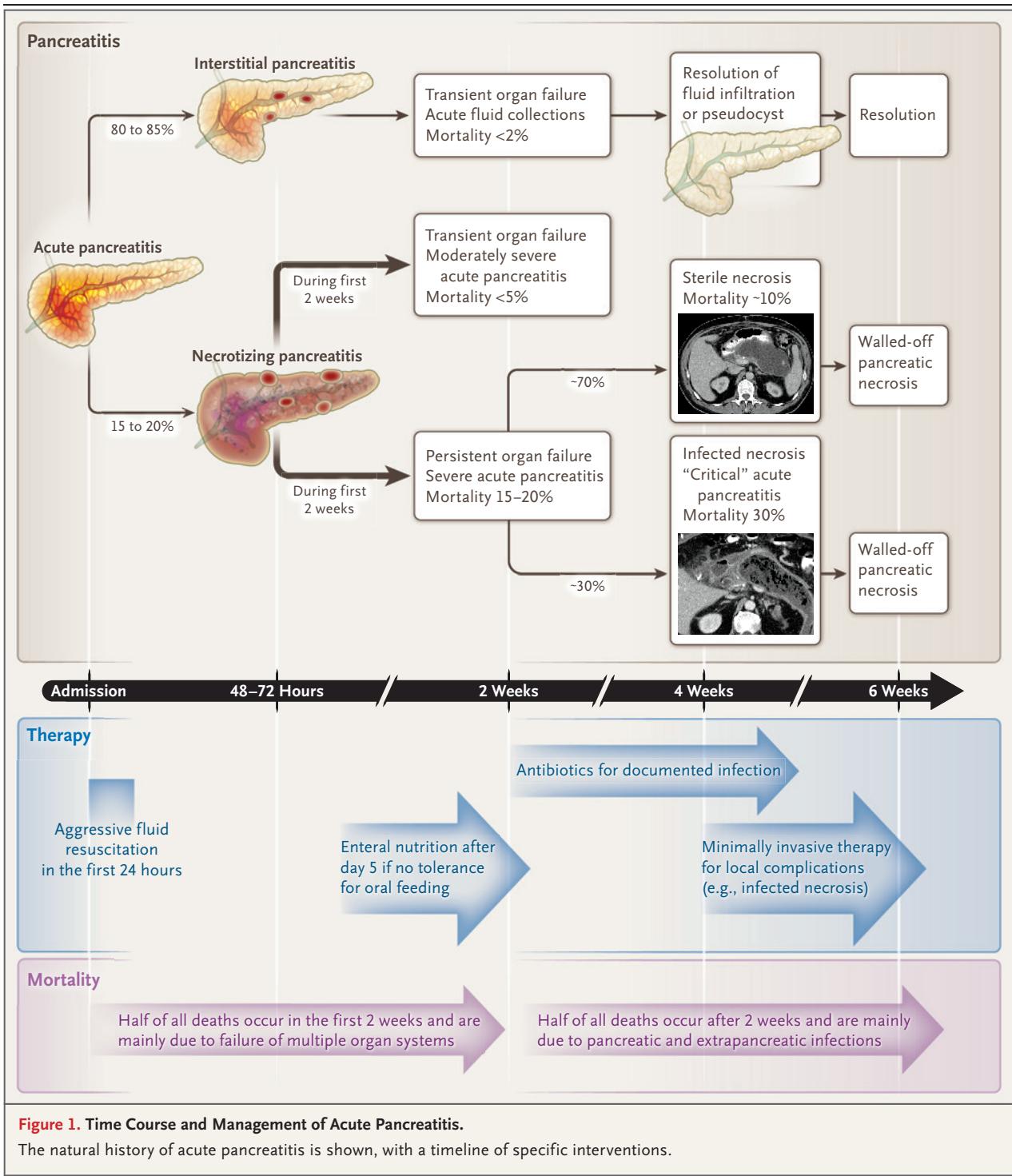
These scoring systems cannot replace ongoing evaluation by an experienced clinician. A few points are worth emphasizing for incorporation into clinical decisions. The presence of the systemic inflammatory response syndrome (SIRS) is usually obvious, although it may not be recognized. SIRS can be diagnosed on the basis of four routine clinical measurements, with findings of two or more of the following values: temperature, below 36°C or above 38°C; pulse, greater than 90 beats per minute; respiratory rate, greater than 20 breaths per minute (or partial pressure of arterial carbon dioxide, <32 mm Hg); and white-cell count, lower than 4000 or higher than 12,000 per cubic millimeter. SIRS that persists for 48 hours or more after the onset of symptoms is indicative of a poor prognosis. Recent guidelines[27,28] recommend using demographic and clinical factors at admission (advanced age, high body-mass index, and coexisting conditions), simple laboratory values at admission and during the next 24 to 48 hours (hematocrit, >44%; blood urea nitrogen level, >20 mg per deciliter [7 mmol per liter]; or creatinine level, >1.8 mg per deciliter [159 μmol per liter]), and the presence of SIRS to identify patients who are at greatest risk for severe disease and most likely to benefit from a high-intensity nursing unit. During the first 48 to 72 hours, a rising hematocrit or blood urea nitrogen or creatinine level, persistent SIRS after adequate fluid resuscitation, or the presence of pancreatic or peripancreatic necrosis on cross-sectional imaging constitutes evidence of evolving severe pancreatitis.[30]

## MANAGEMENT OF ACUTE PANCREATITIS

The essential requirements for the management of acute pancreatitis are accurate diagnosis, appropriate triage, high-quality supportive care, monitoring for and treatment of complications, and prevention of relapse (Fig. 1).

### FLUID RESUSCITATION
Substantial third-space loss and intravascular volume depletion are the basis for many of the negative predictive features of acute pancreatitis

**Figure 1. Time Course and Management of Acute Pancreatitis.**

The natural history of acute pancreatitis is shown, with a timeline of specific interventions.

(hemoconcentration and azotemia).[27-30] On the basis of retrospective studies suggesting that aggressive fluid administration during the first 24 hours reduces morbidity and mortality,[31,32] current guidelines provide directions for early and vigorous fluid administration.[27,28]

Vigorous fluid therapy is most important during the first 12 to 24 hours after the onset of symptoms and is of little value after 24 hours. Administration of a balanced crystalloid solution has been recommended at a rate of 200 to 500 ml per hour, or 5 to 10 ml per kilogram of

body weight per hour, which usually amounts to 2500 to 4000 ml within the first 24 hours.[27,28] One trial suggested the superiority of Ringer's lactate as compared with normal saline in reducing inflammatory markers.[33] Clinical cardiopulmonary monitoring for fluid status, hourly measurement of urine output, and monitoring of the blood urea nitrogen level and hematocrit are practical ways to gauge the adequacy of fluid therapy.

The main, and not inconsequential, risk of fluid therapy is volume overload. Excessive fluid administration results in increased risks of the abdominal compartment syndrome, sepsis, need for intubation, and death.[34,35] Fluid therapy needs to be tailored to the degree of intravascular volume depletion and the cardiopulmonary reserve that is available to handle the fluid. All recommendations regarding fluid resuscitation in patients with acute pancreatitis are based largely on expert opinion. Randomized trials are needed to address the type of fluid, the rate of administration, and the goals of therapy.[36] In the interim, it seems prudent to provide the aggressive regimen of fluid therapy outlined above, as tolerated, in the first 24 hours of illness.

### FEEDING

Total parenteral nutrition is now known to be more expensive, riskier, and no more effective than enteral nutrition in patients with acute pancreatitis.[27,28,37,38] In patients with mild acute pancreatitis who do not have organ failure or necrosis, there is no need for complete resolution of pain or normalization of pancreatic enzyme levels before oral feeding is started.[39] A low-fat soft or solid diet is safe and associated with shorter hospital stays than is a clear-liquid diet with slow advancement to solid foods.[40,41] Most patients with mild acute pancreatitis can be started on a low-fat diet soon after admission, in the absence of severe pain, nausea, vomiting, and ileus (all of which are unusual in mild cases of acute pancreatitis).

A need for artificial enteral feeding may be predicted by day 5, on the basis of symptoms that continue to be severe or an inability to tolerate attempts at oral feeding. Although nasojejunal tube feeding is best for minimizing pancreatic secretion, randomized trials and a meta-analysis[42] have shown that nasogastric or nasoduodenal feeding is clinically equivalent. Simple tube feeding has replaced total parenteral nutrition and feeding through complex, deeply placed intestinal tubes. Whether an elemental or semielemental formula is superior to a polymeric formula is not known.

Total parenteral nutrition should be reserved for the rare cases in which enteral nutrition is not tolerated or nutritional goals are not met. Unfortunately, total parenteral nutrition continues to be used frequently in patients with acute pancreatitis.

Early initiation of nasoenteric feeding (within 24 hours after admission) is not superior to a strategy of attempting an oral diet at 72 hours, with tube feeding only if oral feeding is not tolerated over the ensuing 2 to 3 days.[43] Even patients predicted to have severe or necrotizing pancreatitis do not benefit from very early initiation of enteral nutrition through a tube. Oral feeding can usually be initiated when symptoms improve, with an interval of 3 to 5 days before tube feeding is considered. In patients who cannot tolerate oral feeding after this time, tube feeding can be initiated with the use of a standard nasoduodenal feeding (Dobhoff) tube and a standard polymeric formula.

### ANTIBIOTIC THERAPY

Although the development of infected pancreatic necrosis confers a significant risk of death, well-designed trials[44,45] and meta-analyses[46,47] have shown no benefit of prophylactic antibiotics. Prophylaxis with antibiotic therapy is not recommended for any type of acute pancreatitis unless infection is suspected or has been confirmed (Fig. 1).[27,28] Nonetheless, many patients continue to receive prophylactic antibiotics despite guidelines to the contrary.[48,49]

### ENDOSCOPIC THERAPY

ERCP is used primarily in patients with gallstone pancreatitis and is indicated in those who have evidence of cholangitis superimposed on gallstone pancreatitis. This procedure is also a reasonable treatment in patients with documented choledocholithiasis on imaging or findings strongly suggestive of a persistent bile duct stone (e.g., jaundice, a progressive rise in the results of liver biochemical studies, or a persistently dilated bile duct). ERCP is not beneficial in the absence of these features, in mild cases of acute gallstone pancreatitis, or as a diagnostic test before cholecystectomy.[27,28,50] Endoscopic ultrasonography is used as a platform for minimally invasive treatment of a pancreatic pseudocyst or walled-off pancreatic necrosis (discussed below).

## TREATMENT OF FLUID COLLECTIONS AND NECROSIS

Acute peripancreatic fluid collections (see the Supplementary Appendix) do not require therapy. Symptomatic pseudocysts are managed primarily with the use of endoscopic techniques,[51,52] depending on local expertise.

Necrotizing pancreatitis includes pancreatic gland necrosis and peripancreatic fat necrosis.[25,27,28,53] In the initial phases, the necrotic collection is a mix of semisolid and solid tissue. Over a period of 4 weeks or longer, the collection becomes more liquid and becomes encapsulated by a visible wall. At this point, the process is termed walled-off pancreatic necrosis.[25] Sterile necrosis does not require therapy except in the rare case of a collection that obstructs a nearby viscus (e.g., duodenal, bile duct, or gastric obstruction).

The development of infection in the necrotic collection is the main indication for therapy. Such infections are rare in the first 2 weeks of the illness. The infection is usually monomicrobial and can involve gram-negative rods, enterobacter species, or gram-positive organisms, including staphylococcus. Drug-resistant organisms are increasingly prevalent. The development of fever, leukocytosis, and increasing abdominal pain suggests infection of the necrotic tissue. A CT scan may reveal evidence of air bubbles in the necrotic cavity.

Therapy begins with the initiation of broad-spectrum antibiotics that penetrate the necrotic tissue. Aspiration and culture of the collection are not required. In current practice, efforts are made to delay any invasive intervention for at least 4 weeks to allow for walling off of the necrotic collection — that is, demarcation of the boundary between necrotic and healthy tissue, softening and liquefaction of the contents, and formation of a mature wall around the collection. This delay makes drainage and débridement easier and reduces the risk of complications or death.[54] Delayed intervention is possible in most patients whose condition remains reasonably stable, without the development of a progressive sepsis syndrome. In patients whose condition is not stable, the initial placement of a percutaneous drain in the collection is often enough to reduce sepsis and allow the 4-week delay to be continued.

Nearly 60% of patients with necrotizing pancreatitis can be treated noninvasively and will have a low risk of death.[54,55] For patients in whom infected necrosis develops, a step-up approach with a delay in definitive treatment is now standard. The step-up approach consists of antibiotic administration, percutaneous drainage as needed, and after a delay of several weeks, minimally invasive débridement, if required. This approach is superior to traditional open necrosectomy with respect to the risk of major complications or death,[56] and approximately one third of patients treated with this approach will not require débridement. A number of minimally invasive techniques (e.g., percutaneous, endoscopic, laparoscopic, and retroperitoneal approaches[56,57]) are available to débride infected necrotic tissue in patients with walled-off pancreatic necrosis. A small proportion of patients with infected necrosis can be treated with antibiotics alone.[57,58]

## LONG-TERM CONSEQUENCES OF ACUTE PANCREATITIS

After acute pancreatitis, pancreatic exocrine and endocrine dysfunction develops in approximately 20 to 30% of patients and clear-cut chronic pancreatitis develops in one third to one half of those patients.[2,59,60] Risk factors for the transition to recurrent attacks and chronic pancreatitis include the severity of the initial attack, the degree of pancreatic necrosis, and the cause of acute pancreatitis. In particular, long-term, heavy alcohol use as the cause and smoking as a cofactor dramatically increase the risk of a transition to chronic pancreatitis and reinforce the need for strong efforts to encourage abstinence.

## PREVENTION OF RELAPSE

Cholecystectomy prevents recurrent gallstone pancreatitis. A delay of cholecystectomy for more than a few weeks places the patient at a high (up to 30%) risk for relapse.[61,62] Cholecystectomy performed during the initial hospitalization for mild pancreatitis due to gallstones reduces the rate of subsequent gallstone-related complications by almost 75%, as compared with cholecystectomy performed 25 to 30 days after discharge.[63] For patients with severe or necrotizing pancreatitis, cholecystectomy may be delayed in order to address other clinically significant conditions or provide time for the pancreatic inflammation to diminish, allowing for better operative exposure. For patients who are not considered to be candi-

dates for surgery, endoscopic biliary sphincterotomy will reduce (but not eliminate) the risk of recurrent biliary pancreatitis but may not reduce the risk of subsequent acute cholecystitis and biliary colic.[64]

Patients with alcohol-associated acute pancreatitis who continue to drink alcohol have a high risk of recurrent pancreatitis and, ultimately, chronic pancreatitis.[2,65,66] Half of such patients have a recurrence; the risk is markedly lower for those who are abstinent.[66] A structured, consistent intervention to encourage abstinence is effective at preventing relapse[67] but is often not used. Interventions directed at smoking cessation are also effective preventive measures, since both alcohol and smoking are common risk factors for pancreatitis.

Implicating a specific drug as a cause of acute pancreatitis is difficult, often incorrect, and potentially dangerous if the role of another drug is overlooked.[11] In the absence of any alternative causes, withdrawing an implicated medication may prevent relapse.

Tight control of hyperlipidemia can prevent a relapse of pancreatitis caused by hypertriglyceridemia.[68,69] Serum triglyceride levels will fall in the absence of oral intake of food and fluids. Thus, if it is unclear whether hyperlipidemia caused the acute attack, repeated measurements of blood triglyceride levels after discharge, while the patient is on a stable oral diet, can be informative.

Primary prevention of pancreatitis is possible only in the case of pancreatitis caused by ERCP. ERCP should be avoided in patients who are not likely to benefit from it (e.g., those with suspected sphincter of Oddi dysfunction).[3] Preventive therapies can be used in patients at high risk for post-ERCP pancreatitis on the basis of demographic, clinical, or procedural factors.[70] Two moderately effective therapies are now available: temporary placement of pancreatic duct stents[71] and pharmacologic prophylaxis with nonsteroidal antiinflammatory drugs[72] (Table 1).

## CONCLUSIONS

Acute pancreatitis is an increasingly common clinical problem. New approaches to fluid resuscitation, antibiotic use, nutritional support, and treatment of necrosis have changed management but have not yet been widely adopted. More effective prevention of post-ERCP pancreatitis is possible, and gallstone pancreatitis can be prevented with timely cholecystectomy. The management of acute pancreatitis should continue to improve, as new consensus definitions help to guide clinical research and, even more important, as large clinical consortia collaborate on randomized trials.

### REFERENCES

1. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. Pancreas 2006;33:323-30.
2. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 2013;144:1252-61.
3. Cotton PB, Durkalski V, Romagnuolo J, et al. Effect of endoscopic sphincterotomy for suspected sphincter of Oddi dysfunction on pain-related disability following cholecystectomy: the EPISOD randomized clinical trial. JAMA 2014;311:2101-9.
4. Bertin C, Pelletier AL, Vullierme MP, et al. Pancreas divisum is not a cause of pancreatitis by itself but acts as a partner of genetic mutations. Am J Gastroenterol 2012;107:311-7.
5. DiMagno MJ, Dimagno EP. Pancreas divisum does not cause pancreatitis, but associates with CFTR mutations. Am J Gastroenterol 2012;107:318-20.

6. Coté GA, Imperiale TF, Schmidt SE, et al. Similar efficacies of biliary, with or without pancreatic, sphincterotomy in treatment of idiopathic recurrent acute pancreatitis. Gastroenterology 2012;143(6):1502-1509.e1.
7. Coté GA, Yadav D, Slivka A, et al. Alcohol and smoking as risk factors in an epidemiology study of patients with chronic pancreatitis. Clin Gastroenterol Hepatol 2011;9:266-73.
8. Whitcomb DC, LaRusch J, Krasinskas AM, et al. Common genetic variants in the CLDN2 and PRSS1-PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. Nat Genet 2012;44:1349-54.
9. Apte MV, Pirola RC, Wilson JS. Mechanisms of alcoholic pancreatitis. J Gastroenterol Hepatol 2010;25:1816-26.
10. Phillip V, Huber W, Hagemes F, et al. Incidence of acute pancreatitis does not increase during Oktoberfest, but is higher

than previously described in Germany. Clin Gastroenterol Hepatol 2011;9(11):995-1000.e3.
11. Nitsche C, Maertin S, Scheiber J, Ritter CA, Lerch MM, Mayerle J. Drug-induced pancreatitis. Curr Gastroenterol Rep 2012;14:131-8.
12. Forsmark CE. Incretins, diabetes, pancreatitis and pancreatic cancer: what the GI specialist needs to know. Pancreatology 2016;16:10-3.
13. Bertilsson S, Kalaitzakis E. Acute pancreatitis and use of pancreatitis-associated drugs: a 10-year population-based cohort study. Pancreas 2015;44:1096-104.
14. Whitcomb DC. Genetic risk factors for pancreatic disorders. Gastroenterology 2013;144:1292-302.
15. Sadr-Azodi O, Orsini N, Andrén-Sandberg Å, Wolk A. Abdominal and total adiposity and the risk of acute pancreatitis: a population-based prospective

cohort study. Am J Gastroenterol 2013; 108:133-9.

**16.** Hong S, Qiwen B, Ying J, Wei A, Chaoyang T. Body mass index and the risk and prognosis of acute pancreatitis: a meta-analysis. Eur J Gastroenterol Hepatol 2011; 23:1136-43.

**17.** Krishna SG, Hinton A, Oza V, et al. Morbid obesity is associated with adverse clinical outcomes in acute pancreatitis: a propensity-matched study. Am J Gastroenterol 2015;110:1608-19.

**18.** Andersen DK, Andren-Sandberg A, Duell EJ, et al. Pancreatitis-diabetes-pancreatic cancer: summary of an NIDDK-NCI workshop. Pancreas 2013;42:1227-37.

**19.** Peery AF, Crockett SD, Barritt AS, et al. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. Gastroenterology 2015;149(7):1731-41.e1.

**20.** Hazra N, Gulliford M. Evaluating pancreatitis in primary care: a population-based cohort study. Br J Gen Pract 2014; 64(622):e295-301.

**21.** Spanier B, Bruno MJ, Dijkgraaf MG. Incidence and mortality of acute and chronic pancreatitis in the Netherlands: a nationwide record-linked cohort study for the years 1995-2005. World J Gastroenterol 2013;19:3018-26.

**22.** Lindkvist B, Appelros S, Manjer J, Borgström A. Trends in incidence of acute pancreatitis in a Swedish population: is there really an increase? Clin Gastroenterol Hepatol 2004;2:831-7.

**23.** Pant C, Deshpande A, Olyaee M, et al. Epidemiology of acute pancreatitis in hospitalized children in the United States from 2000-2009. PLoS One 2014;9(5): e95552.

**24.** Wu BU, Johannes RS, Kurtz S, Banks PA. The impact of hospital-acquired infection on outcome in acute pancreatitis. Gastroenterology 2008;135:816-20.

**25.** Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis — 2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-11.

**26.** Dellinger EP, Forsmark CE, Layer P, et al. Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. Ann Surg 2012;256:875-80.

**27.** Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013;108:1400-15.

**28.** Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13: Suppl 2:e1-15.

**29.** Mounzer R, Langmead CJ, Wu BU, et al. Comparison of existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis. Gastroenterology 2012;142:1476-82.

**30.** Yang CJ, Chen J, Phillips AR, Windsor JA, Petrov MS. Predictors of severe and critical acute pancreatitis: a systematic review. Dig Liver Dis 2014;46:446-51.

**31.** Gardner TB, Vege SS, Chari ST, et al. Faster rate of initial fluid resuscitation in severe acute pancreatitis diminishes in-hospital mortality. Pancreatology 2009;9: 770-6.

**32.** Gardner TB, Vege SS, Pearson RK, Chari ST. Fluid resuscitation in acute pancreatitis. Clin Gastroenterol Hepatol 2008; 6:1070-6.

**33.** Wu BU, Hwang JQ, Gardner TH, et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Clin Gastroenterol Hepatol 2011;9(8):710-717.e1.

**34.** Mole DJ, Hall A, McKeown D, Garden OJ, Parks RW. Detailed fluid resuscitation profiles in patients with severe acute pancreatitis. HPB (Oxford) 2011;13:51-8.

**35.** Mao EQ, Tang YQ, Fei J, et al. Fluid therapy for severe acute pancreatitis in acute response stage. Chin Med J (Engl) 2009;122:169-73.

**36.** Haydock MD, Mittal A, Wilms HR, Phillips A, Petrov MS, Windsor JA. Fluid therapy in acute pancreatitis: anybody's guess. Ann Surg 2013;257:182-8.

**37.** Al-Omran M, Albalawi ZH, Tashkandi MF, Al-Ansary LA. Enteral versus parenteral nutrition for acute pancreatitis. Cochrane Database Syst Rev 2010;1:CD002837.

**38.** Yi F, Ge L, Zhao J, et al. Meta-analysis: total parenteral nutrition versus total enteral nutrition in predicted severe acute pancreatitis. Intern Med 2012;51:523-30.

**39.** Eckerwall GE, Tingstedt BB, Bergenzaun PE, Andersson RG. Immediate oral feeding in patients with mild acute pancreatitis is safe and may accelerate recovery — a randomized clinical study. Clin Nutr 2007;26:758-63.

**40.** Jacobson BC, Vander Vliet MB, Hughes MD, Maurer R, McManus K, Banks PA. A prospective, randomized trial of clear liquids versus low-fat solid diet as the initial meal in mild acute pancreatitis. Clin Gastroenterol Hepatol 2007;5:946-51.

**41.** Teich N, Aghdassi A, Fischer J, et al. Optimal timing of oral refeeding in mild acute pancreatitis: results of an open randomized multicenter trial. Pancreas 2010; 39:1088-92.

**42.** Chang YS, Fu HQ, Xiao YM, Liu JC. Nasogastric or nasojejunal feeding in predicted severe acute pancreatitis: a meta-analysis. Crit Care 2013;17:R118.

**43.** Bakker OJ, van Brunschot S, van Santvoort HC, et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. N Engl J Med 2014;371:1983-93.

**44.** Isenmann R, Rünzi M, Kron M, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. Gastroenterology 2004;126:997-1004.

**45.** Dellinger EP, Tellado JM, Soto NE, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. Ann Surg 2007;245:674-83.

**46.** Lim CL, Lee W, Liew YX, Tang SS, Chlebicki MP, Kwa AL. Role of antibiotic prophylaxis in necrotizing pancreatitis: a meta-analysis. J Gastrointest Surg 2015; 19:480-91.

**47.** Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database Syst Rev 2010;5:CD002941.

**48.** Vlada AC, Schmit B, Perry A, Trevino JG, Behrns KE, Hughes SJ. Failure to follow evidence-based best practice guidelines in the treatment of severe acute pancreatitis. HPB (Oxford) 2013;15:822-7.

**49.** Sun E, Tharakan M, Kapoor S, et al. Poor compliance with ACG guidelines for nutrition and antibiotics in the management of acute pancreatitis: a North American survey of gastrointestinal specialists and primary care physicians. JOP 2013;14: 221-7.

**50.** Tse F, Yuan Y. Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. Cochrane Database Syst Rev 2012;5: CD009779.

**51.** Varadarajulu S, Bang JY, Sutton BS, Trevino JM, Christein JD, Wilcox CM. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. Gastroenterology 2013;145(3):583-90.e1.

**52.** Law R, Baron TH. Endoscopic management of pancreatic pseudocysts and necrosis. Expert Rev Gastroenterol Hepatol 2015;9:167-75.

**53.** Bakker OJ, van Santvoort H, Besselink MG, et al. Extrapancreatic necrosis without pancreatic parenchymal necrosis: a separate entity in necrotising pancreatitis? Gut 2013;62:1475-80.

**54.** van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology 2011;141:1254-63.

**55.** Freeman ML, Werner J, van Santvoort HC, et al. Interventions for necrotizing pancreatitis: summary of a multidisciplinary consensus conference. Pancreas 2012;41:1176-94.

**56.** van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med 2010;362:1491-502.

**57.** Bakker OJ, van Santvoort HC, van Brunschot S, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA 2012;307:1053-61.

**58.** Mouli VP, Sreenivas V, Garg PK. Efficacy of conservative treatment, without necrosectomy, for infected pancreatic necro-

sis: a systematic review and meta-analysis. Gastroenterology 2013;144(2):333-340.e2.

**59.** Yadav D, Lee E, Papachristou GI, O'Connell M. A population-based evaluation of readmissions after first hospitalization for acute pancreatitis. Pancreas 2014;43:630-7.

**60.** Sankaran SJ, Xiao AY, Wu LM, Windsor JA, Forsmark CE, Petrov MS. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. Gastroenterology 2015;149(6):1490-1500.e1.

**61.** Gurusamy KS, Nagendran M, Davidson BR. Early versus delayed laparoscopic cholecystectomy for acute gallstone pancreatitis. Cochrane Database Syst Rev 2013; 9:CD010326.

**62.** van Baal MC, Besselink MG, Bakker OJ, et al. Timing of cholecystectomy after mild biliary pancreatitis: a systematic review. Ann Surg 2012;255:860-6.

**63.** da Costa DW, Bouwense SA, Schepers NJ, et al. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. Lancet 2015;386: 1261-8.

**64.** McAlister VC, Davenport E, Renouf E. Cholecystectomy deferral in patients with endoscopic sphincterotomy. Cochrane Database Syst Rev 2007;4:CD006233.

**65.** Sand J, Lankisch PG, Nordback I. Alcohol consumption in patients with acute or chronic pancreatitis. Pancreatology 2007; 7:147-56.

**66.** Pelli H, Lappalainen-Lehto R, Piironen A, Sand J, Nordback I. Risk factors for recurrent acute alcohol-associated pancreatitis: a prospective analysis. Scand J Gastroenterol 2008;43:614-21.

**67.** Nordback I, Pelli H, Lappalainen-Lehto R, Järvinen S, Räty S, Sand J. The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial. Gastroenterology 2009;136: 848-55.

**68.** Valdivielso P, Ramírez-Bueno A, Ewald N. Current knowledge of hypertriglyceridemic pancreatitis. Eur J Intern Med 2014; 25:689-94.

**69.** Yadav D, Pitchumoni CS. Issues in hyperlipidemic pancreatitis. J Clin Gastroenterol 2003;36:54-62.

**70.** Ding X, Zhang F, Wang Y. Risk factors for post-ERCP pancreatitis: a systematic review and meta-analysis. Surgeon 2015; 13:218-29.

**71.** Mazaki T, Mado K, Masuda H, Shiono M. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: an updated meta-analysis. J Gastroenterol 2014;49:343-55.

**72.** Elmunzer BJ, Scheiman JM, Lehman GA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med 2012;366:1414-22.

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