# Acute Pancreatitis

## *Landmark Studies, Management Decisions, and the Future*

*Peter A. Banks, MD*

**Abstract:** A great deal of progress has been made in the last 50 years in the diagnosis and treatment of acute pancreatitis. Many landmark studies have been published and have focused on the classification of acute pancreatitis, markers of severity, important roles of imaging and endoscopy, and improvements in our treatment. This report will review several landmark studies, describe ongoing controversies in management decisions including standards of early fluid resuscitation and appropriate use of enteral feeding, and outline what will be required in the future to improve the care of patients with acute pancreatitis.

**Key Words:** acute pancreatitis, landmark studies in acute pancreatitis, management decisions in acute pancreatitis, classification of acute pancreatitis, treatment of acute pancreatitis

(*Pancreas* 2016;45: 633–640)

Fifty years ago, articles that described the treatment of acute pancreatitis provided very little guidance. The principal concept was putting the gland to rest by prohibiting the intake of food and by removing acid by indwelling nasogastric suction. Mention was made of the need to replace fluid and electrolytes and to ensure adequate urinary output. Additional pointers included treatment of pain by administration of meperidine and use of supplemental oxygen for respiratory care. It was also mentioned that early surgery was needed when an acute intra-abdominal process other than acute pancreatitis could not be excluded or when several days of conservative therapy did not result in clinical improvement in a critically ill patient.[1]

Fifty years ago, there were no landmark studies that stratified the severity of acute pancreatitis, no definitive imaging such as computed tomography (CT) scan, and no formal classification of severity. These were really the dark ages in the treatment of acute pancreatitis.

This report will review some of the landmark studies during the past 50 years that have changed our thinking about the approach to acute pancreatitis and have led to improvements in the care of patients (Table 1). This report will also review management decisions (Table 2) and offer suggestions as to what will be required in the future to further improve the care of patients with acute pancreatitis.

## LANDMARK STUDIES

### Ranson Signs of Severity

In 1974, Ranson et al[2] published 11 signs that stratified severity of acute pancreatitis. Four are measured at admission and 5 during the initial 48 hours (Table 3). An increased number of signs correlated with an increased morbidity and mortality. These signs continue in use at the present time, but to improve patient care, accurate markers of severity are required much earlier than 48 hours and ideally at the time of admission. The early identification of patients who are most likely to have an increased morbidity and mortality will alert the clinician that a higher level of supervision will be required such as in an intensive care unit or pancreas center.

### Balthazar-Ranson CT Scoring System

The first widely used scoring system was published in 1985 by Balthazar et al[3] (Table 4). The stratification of severity from grades A to E correlated with increased number of Ranson signs of severity reflecting increased morbidity and mortality.[3] In 1990, Balthazar et al[4] incorporated evidence of pancreatic necrosis after the use of intravenous contrast into an expanded scoring system (Table 5). The maximum score was 10, which could be achieved by a grade E (4 points) and the presence of more than 50% necrosis (6 points). Lesser scores reflected less severe inflammatory process and less necrosis (or no necrosis at all). Although there are 6 additional radiologic scoring systems that have accuracy essentially equal to the Balthazar-Ranson scoring system in assessing severity,[5] the Balthazar-Ranson scoring system is the one that is used most frequently.

### Computed Tomography–Guided Percutaneous Aspiration

Before the use of CT-guided percutaneous aspiration, patients suspected of harboring pancreatic infection on the basis of increased white blood count and temperature were treated for many weeks with antibiotics that frequently were ineffective. Eventually, patients with persistent elevations in white blood count and temperature would undergo a laparotomy with debridement. This delay of surgical debridement led to marked clinical deterioration resulting in excessive mortality. It was reasoned that if a diagnosis of infected necrosis could be made earlier, more timely surgical debridement would reduce mortality.

In 1987, Gerzof et al[6] published results on the safety and accuracy of CT-guided percutaneous aspiration with Gram stain and culture for the early diagnosis of infected necrosis. In a series of 60 patients strongly suspected of pancreatic infection on the basis of elevated white blood count and temperature, 60% were found to have infected necrosis. All pancreatic infections were confirmed by surgery or catheter drainage. Patients deemed to have sterile pancreatitis on the basis of negative Gram stain and culture showed no subsequent evidence of infection. The technique was also found to be safe in that there were no complications. An additional finding was that pancreatic infection occurred early (within 14 days in 20 of 36 patients). As a result of this study, urgent surgical debridement of infected necrosis became standard of care once infected necrosis was identified on the basis of guided percutaneous aspiration.

Additional experience with this technique further documented its safety and accuracy.[7] Although the rate of infected

From the Center for Pancreatic Disease, Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Boston, MA.
Received for publication October 8, 2015; accepted February 20, 2016.
Reprints: Peter A. Banks, MD, Center for Pancreatic Disease, Brigham and Women's Hospital, 45 Francis St, Boston, MA 02115 (e-mail: PABanks@partners.org).
This author declares no conflict of interest.

**TABLE 1.** Landmark Studies

| |
|---|
| Ranson signs of severity |
| Balthazar-Ranson CT scoring system |
| CT-guided percutaneous aspiration |
| Atlanta Classification of severity-1992 |
| Nonsurgical treatment of severe sterile necrosis |
| Nonsurgical treatment of infected necrosis |
| Persistent organ failure |
| Extrapancreatic necrosis |
| Moderately severe acute pancreatitis |
| Classification of acute pancreatitis-2012 |

necrosis decreased considerably over time, the overall mortality remained at 20%. One reason that mortality of infected necrosis remained considerable was undoubtedly due to the fact that the patient was still experiencing systemic toxicity including persistent organ failure if surgical debridement was performed as soon as infected necrosis was diagnosed.

In recent years, the treatment of infected pancreatic necrosis has changed. At the present time, potent antibiotics are usually able to sterilize the blood stream such that surgical intervention can be safely delayed until organ failure has subsided and infected necrosis has become walled-off.[8] Evidence has accumulated that mortality is decreased among patients with delayed surgery,[9] especially if surgical debridement is deferred for at least 4 weeks.[10–13]

At present, guided percutaneous aspiration is used less frequently than in the 1980s but still plays an important role in selected patients.

## Atlanta Classification of Severity-1992

Before 1992, there was no classification of severity that allowed stratification into high- and low-risk groups. In 1992, Bradley convened a group of 40 pancreatologists in Atlanta, Georgia, to develop a clinical classification of severity of acute pancreatitis (Table 6).[14] This conference stratified severity during hospitalization into 2 categories: mild acute pancreatitis (characterized by the absence of organ failure and local complications) and severe acute pancreatitis (characterized by the presence of organ failure and/or local complications, including necrosis, abscess, and pseudocyst). Organ failure included shock, pulmonary insufficiency, renal failure, and gastrointestinal (GI) bleeding (Table 7). It has become clear that this classification of severity had many deficiencies.[15] First, GI bleeding is rare in acute pancreatitis and should not have been included in the characterization of organ failure. Secondly, it was not yet appreciated that organ failure that is transient (ie, <48 hours in duration) has a very limited impact on morbidity and mortality, whereas organ failure that persists for more than 48 hours is associated with a high mortality of 35% to 50%.[16–18] By including patients with transient and persistent organ failure within the severe category, patients with widely divergent morbidity and mortality were considered to have severe acute pancreatitis. Furthermore, local complications characterized as necrosis, abscess (which is a term that is no longer used), and pseudocyst also have widely divergent morbidity and mortality. A pseudocyst generally causes minimal mortality, whereas necrosis causes substantial mortality when associated with persistent organ failure.

Our biggest failure after the publication of the Atlanta Classification of severity-1992 was not to test its accuracy during the next several years. It was not until after 2000 when inadequacies of the Atlanta Classification in stratifying severity were noted.[15]

**TABLE 2.** Management Decisions

| |
|---|
| Role of markers of severity |
| Early fluid resuscitation |
| Enteral feeding |
| Use of antibiotics |
| Role of ERCP |
| Treatment of necrotizing pancreatitis |

**TABLE 3.** Ranson Signs of Severity[2]

| |
|---|
| At admission |
| Age >55 y |
| White blood cell count >16,000/mm$^3$ |
| Glucose >200 mg/dL |
| LDH >350 IU/L |
| AST >250 U/L |
| During initial 48 hour |
| Hct decrease of >10% points |
| BUN increase of >5 mg/dL |
| Calcium <8 mg/dL |
| $PaO_2$ <60 mm Hg |
| Base deficit >4 mEq/L |
| Fluid sequestration >6 L |

AST indicates aspartate aminotransferase; Hct, hematocrit; LDH; lactate dehydrogenase.

## Nonsurgical Early Treatment of Severe Sterile Necrosis

For many years, the prevailing concept was that patients who were severely ill and did not respond to conservative measures during the first 7 to 10 days of hospitalization should undergo a surgical procedure.[19–23] The overall goal was to remove retroperitoneal fluid and, if possible, necrotic tissue that contained toxic mediators of inflammation. These patients for the most part had sterile pancreatic necrosis.

The first report of nonsurgical treatment of severe necrotizing pancreatitis was published by Bradley et al[24] in 1991. In their series of 11 patients with a moderately high Ranson score that averaged 4, some who required prolonged mechanical ventilation or dialysis, there was no mortality. This concept of avoiding early surgery in severe necrotizing pancreatitis became widespread[13,25–28] such that at present, early surgery is performed only for a complication such as compartment syndrome or necrosis of small or large bowel.

**TABLE 4.** Balthazar-Ranson CT Scoring System[3]

| Grade | Morphology |
|---|---|
| A | Normal-appearing pancreas |
| B | Focal or diffuse enlargement of the pancreas |
| C | Pancreatic gland abnormalities accompanied by mild peripancreatic inflammatory changes |
| D | Fluid collection in a single location, usually within the anterior pararenal space |
| E | ≥2 fluid collections near the pancreas or gas either within the pancreas or within peripancreatic inflammation |

**TABLE 5.** Balthazar-Ranson CT Scoring System[4]: CT Severity Index (0–10)

| CT grade | Score |
|---|---|
| A | 0 |
| B | 1 |
| C | 2 |
| D | 3 |
| E | 4 |
| Necrosis | Score |
| <33% | 2 |
| 33%–50% | 4 |
| >50% | 6 |
| CT grade (0–4) + necrosis (0–6) = total score | |

## Nonsurgical Treatment of Infected Necrosis

During the 1990s, the treatment of infected necrosis also shifted from urgent surgical debridement to a more conservative approach. One reason was that urgent surgical debridement while the patient was still severely ill with organ failure was associated with a high mortality.[10] Another was that more potent antibiotics were successful in curbing systemic toxicity and possibly protecting against organ failure. The possibility that potent antibiotics might actually sterilize infected necrosis was documented in a series of 3 patients in 1996 who had infected pancreatic or peripancreatic necrosis and who survived with antibiotic treatment alone without the need for surgery or catheter drainage.[28] In the late 1990s, Runzi et al presented additional data indicating that patients with infected necrosis could be stabilized successfully with antibiotics. Their series of 28 patients was finally published in *Pancreas* in 2005.[29] Twelve of 28 patients (with an initial Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 15) were stabilized with antibiotic therapy and underwent delayed surgery at a mean of 36 days. Two of these patients died. The remaining 16 patients with an APACHE II score of 18.1 and a Ranson score of 5.9 were treated with antibiotic therapy without surgery. Three required catheter drainage. Two of these 16 patients died. This report established the concept that potent antibiotics should be used as the initial treatment for infected necrosis. Other techniques such as endoscopic debridement and minimally invasive necrosectomy were introduced later.

## Persistent Organ Failure

It was pointed out in a series of articles from 2002 to 2006 that persistent organ failure (defined as organ failure for >48 hours) was associated with a mortality of 36% to 55%, whereas transient organ failure (defined as organ failure that persisted for <48 hours) was associated with a 2% to 3% mortality, identical to the mortality of patients who did not exhibit any organ failure.[16–18]

**TABLE 6.** Atlanta Classification of Severity–1992[8] Severity During Hospitalization

| |
|---|
| Mild acute pancreatitis |
| No organ failure |
| No local complications |
| Severe acute pancreatitis |
| Organ failure and/or local complications |
| Necrosis |
| Abscess |
| Pseudocyst |

**TABLE 7.** Atlanta Classification of Severity–1992[8]

| Organ Failure | Definition |
|---|---|
| Shock | Systolic BP <90 mm Hg |
| Pulmonary insufficiency | $Pa_{O_2}$ ≤60 mm Hg |
| Renal failure | Creatinine >2 mg/dL |
| GI bleeding | >500 mL/24 hr |

BP indicate blood pressure.

Patients who are transferred to hospitals represent a population of severely ill patients with a higher morbidity and mortality than those who are directly admitted to a hospital.[30] In published series, among patients directly admitted to a hospital, the prevalence of persistent organ failure in interstitial pancreatitis is 2%[31] compared with 6% to 15%[32,33] when transferred patients are included. Overall, the prevalence of persistent organ failure is 4% among patients directly admitted to a hospital compared with 26% to 39% when transferred patients are included in the data.[31,33–36]

## Extrapancreatic Necrosis

Most patients with pancreatic necrosis have a combination of pancreatic parenchymal necrosis and extrapancreatic necrosis. On rare occasions, pancreatic necrosis without peripancreatic necrosis has been documented.[37] The concept that patients may have peripancreatic necrosis in the absence of pancreatic parenchymal necrosis was introduced in 1999 in a series of 62 patients with necrotizing pancreatitis, 50 of whom had both pancreatic and extrapancreatic necrosis and 12 (19%) had extrapancreatic necrosis alone.[38] It was determined that patients with extrapancreatic necrosis alone had less severe disease than those with both pancreatic and extrapancreatic necrosis, with a lower APACHE II score (6 vs 10) and a lower mortality (8% vs 20%) but were more severely ill than those with interstitial pancreatitis.[30] In 1 recent series of patients, the prevalence of extrapancreatic necrosis was 49% of all patients with necrotizing pancreatitis.[39]

## Moderately Severe Acute Pancreatitis

The Atlanta Symposium of 1972 distinguished 2 categories of severity in acute pancreatitis: mild acute pancreatitis (characterized by the absence of necrosis and/or organ failure) and severe acute pancreatitis (characterized by organ failure and/or pancreatic necrosis). Investigators at the Mayo Clinic pointed out in a prospective study of 137 patients that there was an intermediate group of patients with morbidity and mortality less than those with severe acute pancreatitis but greater than those with mild acute pancreatitis (Table 8).[40] In this series, mild acute pancreatitis was

**TABLE 8.** Moderately Severe Acute Pancreatitis[40]

| Pancreatitis | % | Symptoms |
|---|---|---|
| Mild acute | 69 | No organ failure, no local complications |
| Moderately severe acute | 20 | No persistent organ failure, local complications present |
| Severe acute | 11 | Persistent organ failure |
| Prospective study (137 patients, excluded transferred patients) | | |

**TABLE 9.** Classification of Acute Pancreatitis–2012,[41] Severity During Hospitalization

| |
|---|
| Mild acute pancreatitis |
| No organ failure |
| No local or systemic complications |
| Moderately severe acute pancreatitis |
| Transient organ failure and/or |
| Local or systemic complications |
| Severe acute pancreatitis |
| Persistent organ failure (≥48 hr) |
| Single organ failure |
| Multiple organ failure |

characterized by the absence of organ failure and local complications; moderately severe acute pancreatitis by local complications (such as prolonged pain, fever, or leucocytosis) but no persistent organ failure; severe acute pancreatitis by persistent organ failure. There was a clear separation in the outcomes of these patients when characterized by need for intensive care unit, total hospital days, and hospital mortality. In particular, mortality of mild and moderately severe acute pancreatitis was 0 and that of severe pancreatitis was 40%. This framework was adapted in the Revised Atlanta Classification of 2012.[41]

## Classification of Acute Pancreatitis of 2012

The Revised Atlanta Classification of 2012 was published in Gut in 2012.[41] This classification represented at least 6 years of ongoing collaboration by the Acute Pancreatitis Classification Working Group further supported internationally by input from 11 pancreatic organizations and many specialists from around the world. The definition of moderately severe acute pancreatitis was extended to include not only patients with transient organ failure and/or those with local complications but also those with systemic complications. Systemic complications were defined as an exacerbation of pre-existing comorbidity, such as chronic lung disease or coronary artery disease. Severe acute pancreatitis was characterized by the persistent organ failure that could either be single organ failure or be multiple organ failure (Table 9). In addition, radiologic definitions were provided for the local complications associated with interstitial and necrotizing pancreatitis (Table 10). In interstitial pancreatitis, radiologic definitions were provided for acute peripancreatic fluid collections and pseudocysts. In necrotizing pancreatitis, definitions were provided for acute necrotic collections and walled-off necrosis.

The Revised Atlanta Classification has been validated in several prospective studies.[33,42] It been challenged by another classification termed determinant-based classification.[34,43,44] Thus far, there does not appear to be a significant advantage of the determinant-based classification.[32,33,35,36,42] Some studies have pointed out potential deficiencies when compared to the Revised Atlanta Classification.[31,35,36,45]

Additional studies will be required to test the accuracy of the Revised Atlanta Classification of 2012. Among issues needed to be evaluated is whether the mortality of infected necrosis with persistent organ failure is the same[31] or higher[44] than that of sterile necrosis with persistent organ failure. In 1 study,[46] mortality correlated more closely with persistent organ failure than with infected necrosis. Also, several reports have suggested that mortality in persistent organ failure occurs mostly among those with multisystem persistent organ failure rather than 1 system persistent organ failure.[31,47]

# MANAGEMENT DECISIONS

## Role of Markers of Severity

Markers of severity, especially those within the first 24 hours and ideally at admission, are critical in the early evaluation of patients with acute pancreatitis. If the patient is determined to have potentially severe disease, their care may require a transfer to a hospital with a center for pancreatic disease or to a higher intensity treatment area such as intensive care unit. Furthermore, accurate markers of severity will allow randomization of patients who have similar severity into prospective clinical studies. Several reports have shown that systemic inflammatory response syndrome (SIRS) during the first 24 hours is a valuable marker of severity.[16,18,48] In particular, in the absence of SIRS during the first 24 hours, the likelihood of increased morbidity and mortality is slight. In the presence of 4 SIRS criteria, the likelihood of severe illness is higher than that if only 2 or 3 criteria are positive.[48]

There are many clinical scoring systems that have been introduced as markers of severity. Among these, APACHE II has proven to be as accurate as any scoring systems that have been developed since that time.[49] It would appear that an APACHE II 8 or higher[17,46] and, in particular, 15 or higher[11,49,50] identifies a group of patients with severe acute pancreatitis. The Bedside Index for Severity in Acute Pancreatitis (BISAP) scoring system has also proven to be an accurate marker of severity with mortality increasing with scores of 3 to 5.[51] The accuracy of the BISAP scoring system has been confirmed in many studies. The Harmless Acute Pancreatitis Score scoring system, developed by Lankisch et al,[52] focuses on 3 criteria at admission that correlate with a harmless episode with minimal morbidity and mortality. The 3 criteria include normal hematocrit, normal creatinine, and absence of guarding or rebound tenderness on physical examination. This scoring system also has been validated in many studies and raises the possibility that patients with a harmless acute pancreatitis score might not require hospitalization but could be treated by fluid resuscitation in the emergency department and discharged to home with appropriate close clinical follow-up.

Single laboratory tests have also been used as markers of severity. In the American Pancreatic Association slide set on acute pancreatitis, it was proposed that a hematocrit level of greater than 50% was an early warning of severity of acute pancreatitis.[53] Baillargeon et al[54] published a report in 1998 that patients with a hematocrit level of 47% or greater at admission and those with a hematocrit level at admission of less than 47% that did not decrease during the first 24 hours were at high risk for pancreatic necrosis. Additional reports suggested that a hematocrit level of 44% or greater at admission was a marker for high risk of pancreatic necrosis and organ failure[55] and that patients with a hematocrit level of 44% or greater at admission who had a further increase of hematocrit during the first 24 hours invariably developed pancreatic necrosis.[56] Additional reports from other institutions with a paucity of referred patients did not confirm this observation. Wu et al[57]

**TABLE 10.** Classification of Acute Pancreatitis–2012[41]

| |
|---|
| Local complications |
| Acute peripancreatic fluid collections |
| Pseudocysts |
| Acute necrotic collections |
| Walled-off necrosis |
| Systemic complications |
| Exacerbation of pre-existing comorbidity |

subsequently showed that the accuracy of hemoconcentration as a marker of severity was attributed to the inclusion of transferred patients who generally have a higher morbidity and mortality than those admitted directly to a hospital. Subsequently, de-Madaria et al[58] have published a report that hemoconcentration is best used as a measure of increased fluid sequestration.

Another single laboratory test that has been used as a marker of severity is blood urea nitrogen (BUN) at admission and trajectory of BUN during the first 24 hours of hospitalization. In a population-based study, Wu et al[59] showed that an increased BUN at admission and an increase of BUN during the first 24 hours correlated with increased mortality in acute pancreatitis. This result has been confirmed in a prospective study from 3 major institutions.[60]

The overall accuracy of markers in predicting persistent organ failure has been evaluated in a study that included APACHE II, Ranson, Glasgow, Harmless Acute Pancreatitis Score, Japanese Severity Score, BISAP, SIRS, BUN, and creatinine.[61] Overall, there was only a modest accuracy at admission and at 48 hours when these markers were subjected to comparison. As such, it seems that we require new approaches to predict persistent organ failure in acute pancreatitis. These approaches could include metabolomics, measurement of cytokines, or intelligence-based data.

## Early Fluid Resuscitation

Textbooks and journal articles have always been emphasizing the importance of vigorous fluid resuscitation but have failed to determine the amount of fluid that would fit this description. The ability of vigorous resuscitation to prevent complications of acute pancreatitis such as pancreatic necrosis and organ failure has been suggested but has not been proven. Concerns about inadequate fluid resuscitation have been that inadequate blood flow to the microcirculation of the pancreas would predispose to pancreatic necrosis and precipitate organ failure. On the other hand, overly aggressive fluid resuscitation might predispose to compartment syndrome, respiratory complications, and possibly even increased infection and mortality. Recent studies have begun to focus on the importance of early fluid resuscitation during the first 24 hours. In 1 study, vigorous early fluid resuscitation was defined as greater than one third of the total 72-hour fluid volume within the initial 24 hours.[62] In a retrospective study of 434 patients, the benefits of early fluid resuscitation compared with later resuscitation was a decreased SIRS in the first 24 hours, reduced organ failure, lower rate of admission to the intensive care unit, reduced length of hospital stay, but no decrease of mortality. In a prospective study of early fluid resuscitation, lactated Ringer's was compared with saline in terms of the effect on C-reactive protein levels and SIRS.[63] It was found that C-reactive protein levels and SIRS were lower after lactated Ringer's when compared with saline. The value of lactated Ringer's might be the fact that it is a more balanced solution than saline. Because lactated Ringer's contains calcium, this solution should not be used among patients with hypercalcemia.

A formula for vigorous fluid resuscitation in acute pancreatitis remains elusive. The present thinking is that among patients who are predicted to have severe acute pancreatitis, it is reasonable to accentuate fluid resuscitation during the first 24 hours, although this may not be necessary among patients predicted to have mild disease. It is also reasonable to monitor trajectory of hematocrit and BUN during the first 12 to 24 hours and make appropriate adjustments in fluid resuscitation on the basis of these values.

## Enteral Feeding

In 1997, a randomized prospective study of 38 patients compared enteral feeding to total parenteral nutrition (TPN). All had necrosis with an overall mortality of 8%.[64] It was determined that enteral feeding was safe and less expensive than TPN but did not decrease the severity of acute pancreatitis. There have been multiple other studies, which have compared enteral feeding with TPN, and overall there seems to be a decrease in morbidity and mortality as a result of enteral feeding.

For many years, it was thought important to introduce food directly into the jejunum (ie, nasojejunal feeding) rather than into the stomach (ie, nasogastric feeding) because of the importance of reducing stimulation of the pancreas by secretin (in response to acid) and by cholecystokinin (in response to food). This concept was challenged in a study in 2005, which compared nasogastric versus nasojejunal feeding in 50 consecutive patients with severe acute pancreatitis.[65] There were no differences in daily median APACHE II score, daily median pain scores, daily median analgesic requirement, and overall mortality. The concept that nasogastric feeding is an acceptable alternative to nasojejunal feeding has gained some acceptance. Early enteral feeding (generally thought to be 2 to 3 days after admission) has been recommended with a view that it stabilizes the gut and thereby prevents bacterial translocation. In a recent study, enteral (nasojejunal) feeding initiated within 24 hours of admission to the hospital was compared with an oral diet at 72 hours among 208 patients, all of whom had APACHE II of higher than 8 (Table 11).[47] The major end points were major infections or death. Early enteral feeding was found not superior to oral diet in respect to major infections or death. Oral diet at 72 hours was tolerated by 69% of patients. It would appear from this study that very early enteral feeding confers no special benefit and that we should consider offering oral diet earlier in even severe acute pancreatitis than is commonly recommended.

## Use of Antibiotics

A number of studies of the role of antibiotic prophylaxis in severe necrotizing pancreatitis that were not double blinded concluded that antibiotic prophylaxis should be used. In 2004 and 2007, 2 multicenter randomized double-blind placebo-controlled studies, one of which used ciprofloxacin/metronidazole and the other meropenem, concluded that there was no difference between patients who received antibiotics and those who received placebo in terms of organ failure, infected pancreatic necrosis, and mortality.[66,67] As such, antibiotic prophylaxis is not recommended in severe acute pancreatitis.

## Role of Endoscopic Retrograde Cholangiopancreatography

The role of early endoscopic retrograde cholangiopancreatography (ERCP) in biliary pancreatitis was clarified in 1997 in a prospective multicenter study in which 126 patients received early ERCP (<72 hours) and 112 patients received conservative therapy.[68] Exclusions included patients with bilirubin level of greater than 5 mg% (presumably excluding patients with biliary obstruction) and those with temperature of 39°C (excluding

**TABLE 11.** Enteral Feeding[47]

| Enteral Feeding (<24 hr) vs oral diet (at 72 hr) |
|---|
| 208 patients (APACHE > 8) |
| Primary end point (major infections or death) |
| Early enteral feeding not superior to oral diet |
| Major infections (25% vs 26%) |
| Death (11% vs 7%) |
| Oral diet at 72 hr (tolerated by 69%) |

those with ascending cholangitis). There was no difference in outcomes in terms of local complications, systemic complications, or mortality. At present, the role of early ERCP in biliary pancreatitis would seem to be restricted to those who are suspected of having ascending cholangitis or obstruction of the common bile duct secondary to gallstones.

## Treatment of Necrotizing Pancreatitis

Surgical treatment of necrotizing pancreatitis in the 1970s included ostomies and sump drains[2,19] and subtotal pancreatectomy with drainage.[20] In the 1980s, debridement of necrosis was accomplished with a variety of techniques.[21–23,69] In 2000, minimally invasive retroperitoneal necrosectomy was reported.[70]

Radiologic drainage of infected pseudocysts and infected necrosis has undergone improvement such that catheter drainage is effective in reducing systemic toxicity before eventual surgery and at times can drain collections definitively without the need for surgery.[13,71–76] Endoscopic drainage of what we now call walled-off necrosis was introduced in 1996 in a report of 10 patients with 50% or more pancreatic necrosis, with endoscopic debridement taking place on an average of 7 weeks after onset of hospitalization[77]; in 9 patients, there was a complete resolution without need of surgery and, in the tenth, there was a need for later necrosectomy. Four of 10 patients did develop infected necrosis, but subsequent to this report, it has been determined that more vigorous debridement including the introduction of the endoscope directly into the walled-off necrosis reduces this complication substantially. These methodologies have been put to the test in a recent randomized prospective trial in Holland involving 88 patients in 19 hospitals in which primary open necrosectomy was compared with a step-up approach (Table 12).[8] The step-up approach involved either percutaneous or endoscopic drainage approximately 4 weeks after hospitalization followed if needed by a minimally invasive retroperitoneal necrosectomy. The advantage of the step-up approach was that 35% were drained successfully by percutaneous or endoscopic means and did not require retroperitoneal necrosectomy and that the step-up approach resulted in less new-onset multiple organ failure, less diabetes, less need for pancreatic enzymes, and was less costly. There was no decrease in mortality, but the study was not powered to evaluate mortality. The present strategy in infected necrosis in centers of pancreatic disease is to use an appropriate antibiotic and to employ a step-up approach rather than urgent surgical debridement.

## Acute Pancreatitis: The Future

There are a number of requirements to improve the care of acute pancreatitis that have not as yet been fulfilled. These include the prevention of acute pancreatitis, accurate early markers of severity, improvement in the treatment of acute pancreatitis, and prevention of progression of acute pancreatitis to chronic pancreatitis. In the future, progress will be made in these goals by increasing research fund, by our strong commitment to basic and clinical research, and by the training of specialists including medical pancreatologists, therapeutic endoscopists, interventional radiologists, and pancreatic surgeons. Multidisciplinary and multihospital collaboration that includes individuals with creative ideas in specialties other than pancreatology will be an important component to our progress. In addition, we will need the strong support of organizations that have a mission to improve patient care including the National Institutes of Health, other organizations that fund research and education, professional societies, the National Pancreas Foundation, and the Digestive Disease National Coalition.

It is my hope that in the years to come, there will be unprecedented progress such that in 50 years, the statement will be made that the years before 2016 were the dark ages in the treatment of acute pancreatitis.

**TABLE 12.** Treatment of Necrotizing Pancreatitis[8]

| Treatment of Infected Necrosis |
|---|
| Randomized prospective trial (19 hospitals, 88 patients) |
| Primary open necrosectomy vs step-up approach |
| Percutaneous or endoscopic drainage |
| Minimally invasive retroperitoneal necrosectomy |
| Advantages of step-up approach |
| 35% did not require retroperitoneal necrosectomy |
| Less new-onset multiple organ failure |
| Less diabetes and less need for pancreatic enzymes |
| Less costly |
| No decreased mortality (19% vs 16%) |

## REFERENCES


1. Banks PA, Janowitz HD. Disease of the pancreas. In: Bennett HD, ed. *The Cyclopedia of Medicine*. 10th ed. Philadelphia, PA: FA Davis; 1966: 181–225.
2. Ranson JH, Rifkind KM, Roses DF, et al. Prognostic signs and the role of operative management in acute pancreatitis. *Surg Gynecol Obstet*. 1974; 139:69–81.
3. Balthazar EJ, Ranson JH, Naidich DP, et al. Acute pancreatitis: prognostic value of CT. *Radiology*. 1985;156:767–772.
4. Balthazar EJ, Robinson DL, Megibow AJ, et al. Acute pancreatitis: value of CT in establishing prognosis. *Radiology*. 1990;174:331–336.
5. Bollen TL, Singh VK, Maurer R, et al. A comparative evaluation of radiologic and clinical scoring systems in the early prediction of severity in acute pancreatitis. *Am J Gastroenterol*. 2012;107:612–619.
6. Gerzof SG, Banks PA, Robbins AH, et al. Early diagnosis of pancreatic infection by computed tomography-guided aspiration. *Gastroenterology*. 1987;93:1315–1320.
7. Banks PA, Gerzof SG, Langevin RE, et al. CT-guided aspiration of suspected pancreatic infection: bacteriology and clinical outcome. *Int J Pancreatol*. 1995;18:265–270.
8. van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med*. 2010; 362:1491–1502.
9. Mier J, León EL, Castillo A, et al. Early versus late necrosectomy in severe necrotizing pancreatitis. *Am J Surg*. 1997;173:71–75.
10. Besselink MGH, Verwer TJ, Schoenmaeckers JP, et al. Timing of surgical intervention in necrotizing pancreatitis. *Arch Surg*. 2007;142: 1194–1201.
11. Rattner DW, Legermate DA, Lee MJ, et al. Early surgical débridement of symptomatic pancreatic necrosis is beneficial irrespective of infection. *Am J Surg*. 1992;163:105–110.
12. Rodriguez JR, Razo AO, Targarona J, et al. Debridement and closed packing for sterile or infected necrotizing pancreatitis. *Ann Surg*. 2008;247: 294–299.
13. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology*. 2011;141:1254–1263.
14. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. *Arch Surg*. 1993;128:586–590.

15. Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006;101:2379–2400.

16. Buter A, Imrie CW, Carter CR, et al. Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis. *Br J Surg*. 2002; 89:298–302.

17. Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. *Gut*. 2004;53:1340–1344.

18. Mofidi R, Duff MD, Wigmore SJ, et al. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. *Br J Surg*. 2006;93:738–744.

19. Warshaw AL, Imbembo AL, Civetta JM, et al. Surgical intervention in acute necrotizing pancreatitis. *Am J Surg*. 1974;127:484–491.

20. Kivilaakso E, Fräki O, Nikki P, et al. Resection of the pancreas for acute fulminant pancreatitis. *Surg Gynecol Obstet*. 1981;152:493–498.

21. Warshaw AL, Jin GL. Improved survival in 45 patients with pancreatic abscess. *Ann Surg*. 1985;202:408–417.

22. Bradley EL 3rd, Fulenwider JT. Open treatment of pancreatic abscess. *Surg Gynecol Obstet*. 1984;159:509–513.

23. Beger HG, Krautzberger W, Bittner R, et al. Results of surgical treatment of necrotizing pancreatitis. *World J Surg*. 1985;9:972–979.

24. Bradley EL 3rd, Allen K. A Prospective longitudinal study of observation versus surgical intervention in the management of necrotizing pancreatitis. *Am J Surg*. 1991;161:19–24.

25. Rau B, Pralle U, Uhl W, et al. Management of sterile necrosis in instances of severe acute pancreatitis. *J Am Coll Surg*. 1995;181:279–288.

26. Büchler MW, Gloor B, Müller CA, et al. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. *Ann Surg*. 2000; 232:619–626.

27. Ashley SW, Perez A, Pierce EA, et al. Necrotizing pancreatitis: contemporary analysis of 99 consecutive cases. *Ann Surg*. 2001;234: 572–589.

28. Dubner H, Steinberg W, Hill M, et al. Infected pancreatic necrosis and peripancreatic fluid collections: serendipitous response to antibiotics and medical therapy in three patients. *Pancreas*. 1996;12:298–302.

29. Runzi M, Niebel W, Goebell H, et al. Severe acute pancreatitis: nonsurgical treatment of infected necroses. *Pancreas*. 2005;30:195–199.

30. Singh VK, Bollen TL, Wu BU, et al. An assessment of the severity of interstitial pancreatitis. *Clin Gastroenterol Hepatol*. 2011;9:1098–1103.

31. Kadiyala V, Suleiman SL, McNabb-Baltar J, et al. The Atlanta classification, revised Atlanta classification, and determinant-based classification of acute pancreatitis: which is best at stratifying outcomes? *Pancreas*. 2016;45:510–515.

32. Anand G, Hutfless SM, Akshintala VS, et al. A population-based evaluation of severity and mortality among transferred patients with acute pancreatitis. *Pancreas*. 2014;43:1111–1116.

33. Talukdar R, Bhattacharrya A, Rao B, et al. Clinical utility of the revised Atlanta classification of acute pancreatitis in a prospective cohort: have all loose ends been tied? *Pancreatology*. 2014;14:257–262.

34. Thandassery RB, Yadav TD, Dutta U, et al. Prospective validation of 4-category classification of acute pancreatitis severity. *Pancreas*. 2013;42: 392–396.

35. Nawaz H, Mounzer R, Yadav D, et al. Revised Atlanta and determinant-based classification: application in a prospective cohort of acute pancreatitis patients. *Am J Gastroenterol*. 2013;108:1911–1917.

36. Acevedo-Piedra NG, Moya-Hoyo N, Rey-Riveiro M, et al. Validation of the determinant-based classification and revision of the Atlanta classification systems for acute pancreatitis. *Clin Gastroenterol Hepatol*. 2014;12:311–316.

37. Casey JE, Porter KA, Langevin RE, et al. Clinical features and natural history of central cavitary necrosis. *Pancreas*. 1993;8:141–145.

38. Sakorafas GH, Tsiotos GG, Sarr MG. Extrapancreatic necrotizing pancreatitis with viable pancreas: a previously under-appreciated entity. *J Am Coll Surg*. 1999;188:643–648.

39. Bakker OJ, van Santvoort H, Besselink MG, et al. Extrapancreatic necrosis without pancreatic parenchymal necrosis: a separate entity in necrotising pancreatitis? *Gut*. 2013;62:1475–1480.

40. Talukdar R, Clemens M, Vege SS. Moderately severe acute pancreatitis prospective validation of this new subgroup of acute pancreatitis. *Pancreas*. 2012;41:306–309.

41. 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;62:102–111.

42. Choi JH, Kim MH, Oh D, et al. Clinical relevance of the revised Atlanta classification focusing on severity stratification system. *Pancreatology*. 2014;14:324–329.

43. Dellinger EP, Forsmark CE, Layer P, et al. Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. *Ann Surg*. 2012;256:875–880.

44. Petrov MS, Shanbhag S, Chakraborty M, et al. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology*. 2010;139:813–820.

45. Guo Q, Li M, Chen Y, et al. Determinant-based classification and revision of the Atlanta classification, which one should we choose to categorize acute pancreatitis? *Pancreatology*. 2015;4:331–336.

46. Guo G, Li A, Xia Q, et al. The role of organ failure and infection in necrotizing Pancreatitis: a prospective study. *Ann Surg*. 2014;259: 1201–1207.

47. 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;371:1983–1993.

48. Singh VK, Wu BU, Bollen TL, et al. Early systemic inflammatory response syndrome is associated with severe acute pancreatitis. *Clin Gastroenterol Hepatol*. 2009;7:1247–1251.

49. Larvin M, McMahon MJ. APACHE-II score for assessment and monitoring of acute pancreatitis. *Lancet*. 1989;2:201–205.

50. Karimgani I, Porter KA, Langevin RE, et al. Prognostic factors in sterile pancreatic necrosis. *Gastroenterology*. 1992;103:1636–1640.

51. Wu BU, Johannes RS, Sun X, et al. The early prediction of mortality in acute pancreatitis: a large population-based study. *Gut*. 2008;57: 1698–1703.

52. Lankisch PG, Weber-Dany B, Hebel K, et al. The harmless acute pancreatitis score: a clinical algorithm for rapid initial stratification of nonsevere disease. *Clin Gastroenterol Hepatol*. 2009;7:702–705.

53. Banks PA, Burrell MI, Sweeting JG, et al. *Pancreatitis. American Gastroenterological Association Clinical Teaching Project, Unit 5*. Timonium, MD: Milner-Fenwick, Inc; 1990.

54. Baillargeon JD, Orav J, Ramagopal V, et al. Hemoconcentration as an early risk factor for necrotizing pancreatitis. *Am J Gastroenterol*. 1998;93: 2130–2134.

55. Brown A, Orav J, Banks PA. Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis. *Pancreas*. 2000;20:367–372.

56. Brown A, Baillargeon JD, Hughes MD, et al. Can fluid resuscitation prevent pancreatic necrosis in severe acute pancreatitis? *Pancreatology*. 2002;2:104–107.

57. Wu BU, Johannes RS, Conwell DL, et al. Early hemoconcentration predicts increased mortality only among transferred patients with acute pancreatitis. *Pancreatology*. 2009;9:639–643.

58. de-Madaria E, Banks PA, Moya-Hoyo N, et al. Early factors associated with fluid sequestration and outcomes of patients with acute pancreatitis. *Clin Gastroenterol Hepatol*. 2014;12:997–1002.

59. Wu BU, Johannes RS, Sun X, et al. Early changes in blood urea nitrogen predict mortality in acute pancreatitis. *Gastroenterology*. 2009;137:129–135.

60. Wu BU, Bakker OJ, Papachristou GI, et al. Blood urea nitrogen in the early assessment of acute pancreatitis: an international validation study. *Arch Intern Med*. 2011;171:669–676.

61. 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;142:1476–1482.

62. Warndorf MG, Kurtzman JT, Bartel MJ, et al. Early fluid resuscitation reduces morbidity among patients with acute pancreatitis. *Clin Gastroenterol Hepatol*. 2011;9:705–709.

63. 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;9:710–717.

64. Kalfarentzos F, Kehagias J, Mead N, et al. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. *Br J Surg*. 1997;84:1665–1669.

65. Eatock FC, Chong P, Menezes N, et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. *Am J Gastroenterol*. 2005;100:432–439.

66. 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;245:674–683.

67. Isenmann R, Runzi 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.

68. Fölsch UR, Nitsche R, Lüdtke R, et al. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis. *N Engl J Med*. 1997;336:237–242.

69. Davidson ED, Bradley EL 3rd. "Marsupialization" in the treatment of pancreatic abscess. *Surgery*. 1981;89:252–256.

70. Carter CR, McKay CJ, Imrie CW. Percutaneous necrosectomy and sinus tract endoscopy in the management of infected pancreatic necrosis: an initial experience. *Ann Surg*. 2000;232:175–180.

71. Karlson KB, Martin EC, Fankuchen EI, et al. Percutaneous drainage of pancreatic pseudocysts and abscesses. *Radiology*. 1982;142:619–624.

72. Gerzof SG, Johnson WC, Robbins AH, et al. Percutaneous drainage of infected pancreatic pseudocysts. *Arch Surg*. 1984;119:888–893.

73. vanSonnenberg E, Wittich GR, Casola G, et al. Complicated pancreatic inflammatory disease: diagnostic and therapeutic role of interventional radiology. *Radiology*. 1985;155:335–340.

74. Freeny PC, Lewis GP, Traverso LW, et al. Infected pancreatic fluid collections: percutaneous catheter drainage. *Radiology*. 1988;167:435–441.

75. vanSonnenberg E, Wittich GR, Casola G, et al. Percutaneous drainage of infected and noninfected pancreatic pseudocysts: experience in 101 cases. *Radiology*. 1989;170:757–761.

76. Freeny PC, Hauptmann E, Althaus SJ, et al. Percutaneous CT-guided catheter drainage of infected acute necrotizing pancreatitis: techniques and results. *AJR Am J Roentgenol*. 1998;170:969–975.

77. Baron TH, Thaggard WG, Morgan DE, et al. Endoscopic therapy for organized pancreatic necrosis. *Gastroenterology*. 1996;111:755–764.