Uncomplicated Acute Pancreatitis

Evidenced-Based Management Decisions

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KEYWORDS

• Pancreatitis • Acute • Severity • Management

KEY POINTS

- Acute pancreatitis is among the most common gastrointestinal disorders requiring hospitalization.
- Early goal-directed fluid resuscitation with lactated Ringer solution remains the cornerstone of therapy the management of mild acute pancreatitis.
- Non-opioid analgesics should be considered in the management of pain in acute pancreatitis.
- A low-fat, low-residue diet can be used for initial re-feeding after resolution of nausea, emesis and abdominal pain.
- There is no role of prophylactic antibiotics in the setting of necrotizing pancreatitis.

INTRODUCTION AND EPIDEMIOLOGY

Acute pancreatitis (AP) is among the most common gastrointestinal disorders requiring hospitalization worldwide with an annual incidence of 13 to 45 cases per 100,000 persons.[1] In the United States, AP resulted in 275,000 hospitalizations in 2012 with aggregate costs of $2.6 billion.[2] Recent National Hospital Discharge Surveys suggests that although there has been an increase in AP admissions, the overall mortality rate has remained around 2%.[3]

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DIAGNOSIS OF ACUTE PANCREATITIS

According to the revised Atlanta classification, AP is diagnosed if two or more of the three clinical features listed at the top of **Table 1** are present.[4] There are additional considerations listed under each of these clinical features that are importance to the practitioner (see **Table 1**).

ELEVATION OF PANCREATIC ENZYMES WITHOUT ACUTE PANCREATITIS

Lipase is elevated to three times the upper limit of normal in many nonpancreatic conditions as summarized in **Table 2**.[5–7] In a large study of cardiovascular safety in patients with type 2 diabetes, 22.7% were noted to have asymptomatic amylase and lipase elevation.[8] Abdominal imaging should be considered when a patient without clear risk factors for AP presents with upper abdominal pain and elevated pancreatic enzymes because neither are specific for AP.

EVALUATION OF THE CAUSE OF ACUTE PANCREATITIS

Establishing the cause of AP ensures appropriate management and proper health care resource use. The two most common causes of AP are biliary (40%–70%) and alcohol use (25%–35%).[1,9] Other causes include metabolic factors, such as hypertriglyceridemia (HTG), hypercalcemia, drug induced, autoimmune, hereditary/genetic, and anatomic abnormalities.

Biliary Tract Stones and/or Sludge

Biliary tract stones and/or sludge are the most common cause of AP. Approximately 7% of the US adult population has gallstones but only 0.1% to 0.3% develop associated complications including acute cholecystitis, choledocholithiasis, or acute biliary pancreatitis.[10,11] All patients presenting with their first episode of AP should undergo abdominal ultrasonography.[12] If abdominal ultrasonography does not identify stones or sludge, an alanine aminotransferase greater than three times the upper limit of normal has greater than 95% positive predictive value for acute biliary pancreatitis.[13] Patients with elevated liver enzymes on Day 1 were found to have low risk of AP recurrence after cholecystectomy (9%), but the risk of AP recurrence is higher among those without elevated liver enzymes (34%) or in those without gallbladder stone/sludge (61%).[14]

The risk of pancreatitis among heavy users of alcohol ranges from 2% to 5%.[15,16] It should be highlighted that most heavy drinkers do not develop pancreatitis, which suggests that there are other factors that drive risk. Alcohol can modify the risk of AP from other etiologies including genetic mutations, hyperlipidemia, and drug-induced pancreatitis.[1] There is a dose-dependent relationship between alcohol and the risk of AP with various reports describing an increased risk of pancreatitis in individuals consuming greater than 14 beers per week.[16,17]

Smoking Tobacco

Smoking tobacco has been identified to be independent risk factor for pancreatitis. The risk is dose dependent, particularly with a 15 pack-year history.[18] However, with two decades of smoking cessation, the risk is noted to be reduced to the levels of never smokers.[19] Smoking is also known to modify risk of AP from other etiologies and combined use of smoking and alcohol can synergistically increase the risk of AP.[1]

Table 1
Diagnosis of acute pancreatitis

Clinical Features	Upper Abdominal Pain	Elevation of Amylase or Lipase ≥3 Times the Upper Limit of Normal	Abdominal Imaging
Considerations	• Most commonly localized to the epigastrium with or without radiation to the back. • Location of pain is nonspecific because of viscerosomatic sensory convergence in the spinal cord and can therefore be confused with other conditions that cause upper abdominal pain.	• Amylase has short half-life and is normal by 24 h but lipase can remain elevated for 8–14 d, longer in the setting of renal dysfunction. Lipase has higher sensitivity and because of wider window of detection is more suitable for delayed presentations. • Lipase alone is recommended for the diagnosis of AP.[80,81] • The reference range of lipase varies based on laboratory assay used. • Lipase levels should only be used to diagnose AP and should not be checked each day of hospitalization because it does not correlate with prognosis, clinical improvement, or disease severity.[82] • Higher triglyceride levels (>1000 mg/dL) are associated with higher lipase and lower amylase level because of interference with the lipase assay, and serial dilutions are needed for accurate measurements in this setting.[23]	• CECT is the most commonly used imaging modality in the setting of AP and has a sensitivity and specificity of more than 90% for the diagnosis of AP.[83] • Consider imaging to assess for other causes when there is diagnostic uncertainty or assess for complications especially when there is inadequate response to initial treatment. • Caution must be used when mild AP changes are reported on imaging studies because radiologists are not typically blinded to laboratory studies and this results in interpretation bias. • IAP/APA guidelines recommend the optimal timing and type of CECT.[68] • Among patients with renal insufficiency or with contrast allergy T2-weighted MRI is used to accurately diagnose pancreatic necrosis.[84]

Abbreviations: APA, American Pancreatic Association; CECT, contrast-enhanced computerized tomography; IAP, International Association of Pancreatology.

Table 2
Elevation of amylase and lipase in the absence of acute pancreatitis

Gastrointestinal	Nongastrointestinal
Elevated amylase or lipase	Elevated amylase or lipase
Gastroenteritis	Ectopic pregnancy
Peptic ulcer disease	Diabetes type 1 and type 2
Bowel perforation	Sarcoidosis
Bowel ischemia	Intracranial hemorrhage or traumatic brain injury
Bowel obstruction	Renal impairment
Pancreatic pseudocyst	Ruptured abdominal aortic aneurysm
Cholangitis	Opioid analgesics
Cholecystitis	Elevated amylase
Post endoscopic retrograde cholangiopancreatography (without pancreatitis)	Parotitis
	Macroamylasemia
Peritonitis	Ovarian cyst or cystic neoplasm
Celiac disease	Carcinoma of the lung

Hypertriglyceridemia

HTG is the third leading cause of AP in the United States and is identified as the cause of AP in up to 14% of AP cases, and up to 56% cases of AP during pregnancy.[20,21] HTG can result from primary (genetic) and secondary disorders of lipoprotein lipase metabolism. Frederickson type I (high chylomicrons), now known as familial chylomicronemia syndrome, type IV (high very-low-density lipoprotein), and type V (high chylomicrons and very-low-density lipoprotein) can cause severe HTG and increase the risk of AP. Secondary disorders including poorly controlled diabetes, medications, alcohol use, hypothyroidism, and pregnancy can result in HTG and AP. Triglyceride level of greater than 885 mg/dL was suspected to increase the risk of AP but a recent large epidemiologic study found that levels as low as 177 mg/dL are associated with an increased risk of AP but the absolute risk is still low.[22–24] The risk of AP at triglyceride levels greater than 1000 mg/dL is 5% and greater than 2000 mg/dL is 15%.[22] Approximately one-fourth of the adult population in the United States has triglycerides levels greater than 176 mg/dL.[25] Increasing triglyceride levels have been shown to positively correlate with the risk of persistent organ failure, regardless of the cause of AP, likely because of triglyceride-related lipotoxicity.[24] Although the initial treatment of severe HTG involves supportive measures commonly instituted in patients with AP, specific treatments, such as apheresis, heparin, and insulin, have also been used. It should be noted that HTG-mediated injury leading to AP has already occurred by the time a patient is admitted to the hospital; therefore, interventions to acutely reduce the triglyceride level, although commonplace, are not evidence based. Data from two large US health databases have shown that among the patients with severe HTG, reducing the triglyceride level to less than 200 mg/dL resulted in the lowest rates of recurrent AP on follow-up.[26] Long-term levels of triglycerides should be maintained less than 200 mg/dL through a combination of diet, exercise, fibrates, and omega-3 fatty acids.[27]

Pancreas Divisum

Pancreas divisum is the most common congenital anomaly in humans and is present in around 7% to 8% of the white population with more than 95% being asymptomatic.[28] Pancreas divisum does not modify the natural history of idiopathic recurrent

AP and is more likely to be an incidental finding.[29] No clear association between AP and pancreas divisum has been identified, in the absence of CFTR or SPINK1, or PRSS1 mutations.[30] Pancreatic endotherapy including repeated pancreatic duct stent placements and pancreatic sphincterotomies are therefore not recommended for patients with idiopathic AP and pancreas divisum.

Idiopathic Pancreatitis

Idiopathic pancreatitis is defined as AP where the cause is not apparent after history, laboratory, and imaging studies are obtained. Endoscopic ultrasound because of its higher sensitivity must be considered to evaluate for microlithiasis and ampullary or pancreatic cancer, particularly in patients who are older, smoke, and have new-onset diabetes and/or unexplained weight loss.[31] Hereditary/genetic pancreatitis is considered among patients in whom the cause continues to be unidentified, particularly in patients less than 35 years of age.[32]

CLASSIFICATION OF DISEASE SEVERITY AND RISK STRATIFICATION

After a diagnosis of AP is made, it is important to identify which patients either have or are at risk of severe AP. Severe AP occurs in 15% to 20% of patients with AP, which is the incidence reported from academic centers; however, the transfer of patients to these centers likely results in an overestimation of severe AP.[33] **Table 3** summarizes the definitions of disease severity in AP based on the most recent classification systems.[4,34,35] The revised Atlanta classification defines organ failure as a score of two or more in any one of the organ systems (renal, respiratory, and cardiovascular) using the modified Marshall scoring system. Clinicians should recognize that most patients with severe AP do not present with organ failure or local complications at the time of admission and these could develop as a result of inadequate resuscitation or lack of identification of early signs.[36] The ability to predict the severity of disease early in the course of hospitalization allows for triage to advanced level of care in the intensive care unit setting, aggressive fluid therapy, and enteral nutrition. Although there have been numerous clinical and radiologic scoring systems developed to predict the severity of AP, they are associated with high negative but low positive predictive value for severe AP.[37]

The bedside index for severity in AP scoring system consists of five parameters: (1) blood urea nitrogen greater than 25 mg/dL, (2) impaired mental status, (3) presence of the systematic inflammatory response syndrome (SIRS), (4) age greater than 60 years, and (5) pleural effusions.[38] A score of three or more in the first 24 hours has been

Table 3
Acute pancreatitis severity classification systems

Classification System	Disease Severity	Criteria
Atlanta Classification 1992	Mild	No organ failure and no local complications
	Severe	Organ failure and/or local complications
Revised Atlanta Classification 2007 (published 2013)	Mild	No organ failure and no local or systemic complications
	Moderate	Transient organ failure and/or local complications
	Severe	Persistent organ failure
Determinant-Based Classification 2012	Mild	No (peri)pancreatic necrosis and no organ failure
	Moderate	Sterile necrosis and/or transient organ failure
	Severe	Infected necrosis or persistent organ failure
	Critical	Infected necrosis and persistent organ failure

shown to be associated with a 5% to 20% risk of mortality.[38] Papachristou and colleagues[39] compared several scoring systems and found the prognostic accuracy of bedside index for severity in AP to be similar to other scoring systems but simpler to use. The simplicity of SIRS has also made it attractive as a single biomarker for assessing disease activity.[40] SIRS on Day 1 of admission has also been shown to predict severe AP with high sensitivity (85%–100%) and the absence of SIRS on Day 1 was associated with a high negative predictive value (98%–100%).[41] The recently developed and prospectively validated Pancreatitis Activity Scoring System uses organ failure, SIRS, abdominal pain, requirement for opioids, and ability to tolerate oral intake as a dynamic measure of disease activity in AP.[42]

INITIAL MANAGEMENT OF ACUTE PANCREATITIS

Indications for Early Discharge Versus Monitored or Intensive Level of Care

The incidence of early readmission in AP is high, occurring in 19% of patients.[43] On a multivariable analysis, moderate to heavy alcohol use (odds ratio, 10.1), discharge on less than a solid diet (odds ratio, 23.8), and persistent gastrointestinal symptoms, such as nausea/emesis (odds ratio, 44.2), were determined to be the strongest risk factors for early readmission. Among patients who require prolonged hospitalization, most are managed at specialty centers experienced in the management of AP. However, patients with severe AP should be appropriately triaged and considered for transfer to tertiary centers.

Fluid Therapy in Acute Pancreatitis Management

Fluid therapy remains the cornerstone of managing AP. The fluid losses are significant in AP and result from multiple factors inherent to the pathophysiology of AP, including third spacing, vomiting, reduced oral intake, respiratory losses, and diaphoresis. This is further compounded by the microangiopathic effects of cytokines and inflammatory mediators of AP leading to reduced vascular resistance similar to sepsis, resulting in reduced pancreatic blood flow, cellular death, and necrosis, which causes a “second hit” on the pancreas with activation of the enzyme cascade.[44] Hemoconcentration, a marker of fluid losses, is associated with an increased risk of pancreatic necrosis and organ failure.[45] Aggressive early hydration is therefore thought to augment circulatory support to prevent complications of AP, such as necrosis or organ failure.[46]

Two well-conducted randomized controlled trials (RCTs) demonstrated lactated Ringer solution (LR) to be beneficial over normal saline and one RCT demonstrated aggressive or goal-directed hydration with LR to be more beneficial compared with standard hydration with LR among patients with mild AP.[47–49] In the setting of AP, LR has additional benefits because of a direct inhibitory effect on macrophage-mediated inflammation when compared with normal saline.[49,50]

Based on the pathophysiology of AP, fluid therapy is thought to play the most crucial role during the first 12 to 24 hours and early hydration in the emergency room is of utmost importance.[46] The rate and volume of fluid therapy is based on conflicting guidelines and data from two RCTs (**Table 4**). Furthermore, few of the previously conducted studies suggested increased morbidities, such as respiratory complications, compartment syndrome, and even mortality from aggressive early hydration in the first 48 hours, but these studies included much sicker patients and could be caused by reverse causation.[51,52] Aggressive hydration requires additional caution among elderly patients and those with cardiopulmonary and renal comorbidities who are more susceptible to complications from volume overload.

Table 4
Fluid type and rate in recent guidelines and RCT

	Initial Fluid Administration	Maintenance Fluid Administration
Guideline		
AGA guidelines, 2018	Goal directed	Goal-directed maintenance
ACG guidelines, 2013	Goal directed Aggressive 250–500 mL/h crystalloid	Goal-directed maintenance
IAP/APA guidelines, 2013	Goal directed 5–10 mL/kg/h	Goal-directed maintenance
RCT author		
de-Madaria et al,[49] 2018	Goal directed Aggressive LR/NS 15 mL/kg bolus Standard LR/NS 10 mL/kg bolus	Aggressive LR/NS 1.2 mL/kg/h Standard LR/NS 1 mL/kg/h
Buxbaum et al,[48] 2017	Goal directed Aggressive LR 20 mL/kg bolus Standard LR 10 mL/kg bolus	Aggressive LR 3 mL/kg/h Standard LR 1.5 mL/kg/h
Wu et al,[47] 2011	Goal directed LR/NS 20 mL/kg bolus Standard physician directed LR/NS	Goal directed LR/NS 3 mL/kg/h or 1.5 mL/kg/h

Abbreviations: ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; APA, American Pancreatic Association; IAP, International Association of Pancreatology; NJ, nasojejunal; NS, normal saline.

Pain Control in Acute Pancreatitis

Pain is a key symptom of AP with diagnostic and prognostic value. It was noted that the duration of pain before hospitalization impacts the severity of AP among patients with hemoconcentration at the time of admission.[53] Hypovolemia and fluid losses associated with AP can result in pain from visceral ischemia; therefore, adequate fluid therapy as discussed previously is important. A mild episode of AP might be adequately treated with nonsteroidal anti-inflammatory drugs alone[54] and for appropriate pain control for more severe episode, more potent opioid analgesics are typically used.[55] A Cochrane review of trials of nonopioids and opioids analgesics found similar improvements in pain at 2 days for all analgesics.[56] A prospective cohort study reported an increased risk of gastrointestinal dysmotility among patients with AP receiving opioid analgesics compared with those receiving nonopioid analgesics and this results in delays in oral refeeding and impacts quality of life.[57] Nonopioid analgesics should therefore be considered for pain control in patients with AP.

Role of Endoscopy in Biliary Acute Pancreatitis

Biliary pancreatitis is caused by obstruction of the ampulla of Vater by a stone, which results in increased pancreatic ductal pressure and reflux of bile into the pancreatic duct that activates pancreatic enzymes and the inflammatory cascade. Most stones pass spontaneously into the duodenum but a minority of these result in obstruction and thus require removal.[58] Endoscopic retrograde cholangiopancreatography (ERCP) is a therapeutic modality to relieve persistent ductal obstruction from a biliary stone. However, it must be noted that cholestasis can also be caused by ampullary edema from a previously passed stone or from edema causing compression of the duct in the head of pancreas and, therefore, appropriate patient selection is needed

to identify those who require ERCP.[59] A meta-analysis of eight RCTs comparing early ERCP versus conservative management in biliary AP showed that urgent ERCP does not impact important clinical outcomes, such as mortality, organ failure, and pancreatic necrosis.[60] Urgent ERCP is therefore not recommended in the setting of cholestasis alone without cholangitis. The impact of endoscopic sphincterotomy on complications in these patients is the subject of an ongoing trial in the Netherlands.[61]

Cholecystectomy in Biliary Acute Pancreatitis

If cholecystectomy is delayed after an initial hospitalization for biliary AP, several cohort studies have demonstrated that the risk of recurrent biliary complications, including recurrent AP, acute cholecystitis, or choledocholithiasis is around 17% at 6 months.[62] Biliary sphincterotomy alone has been shown to reduce the risk of recurrent AP but no other biliary complications in those with a gallbladder.[63] Cholecystectomy after an episode of biliary AP is recommended by current guidelines with high degree of adherence but the timing of cholecystectomy has been much debated.[64] Three RCTs[62,65,66] have evaluated the timing of cholecystectomy after biliary AP and suggested that cholecystectomy is safely performed during the index hospitalization for mild AP. In the setting of moderate to severe AP, especially with fluid collections, surgery should be delayed until the acute inflammation/fluid collections have resolved or stabilized.[67] Delaying surgery in the setting of pancreatic necrosis or severe AP reduces the risk of surgical complications. The timing of surgery in these situations should be delayed to around 6 weeks.[68]

Nutrition in Acute Pancreatitis

Nutrition therapy in AP pertains to the timing of reinitiating oral feeding or other mode of enteral feeding, composition of feeding, and/or need for parenteral nutrition.

Timing of reinitiating oral feeding

Clinical practice has historically focused on the tolerance of oral feeding as a criterion for discharge and maintaining strict nothing by mouth status until the resolution of abdominal pain.[69] Nothing by mouth status is initiated to reduce the stimulation of pancreatic secretion and prevent further activation of the pancreatic enzymes and resulting inflammatory response. However, there is little evidence to support this concept.[70] There is also increased concern regarding intestinal mucosal atrophy with nothing by mouth status thereby affecting the gut-mucosal barrier, which increases the risk of transmigration of gut flora. Early initiation of oral feeding has been shown in multiple studies to reduce the risk of infectious complications of AP and overall morbidity and mortality associated with severe AP.[12] However, AP can result in gastrointestinal dysmotility and ileus leading to nausea and vomiting, which limits the tolerance of oral intake.

A recent systematic review of 11 RCTs comparing early with delayed feeding in patients with mild to moderate AP[71] demonstrated that early feeding reduces length of hospital stay and with no increased risk of adverse events. A soft low-fat, low-residue diet was noted to provide more calories compared with clear liquid diet, without any increase in pain recurrence rates.[72] Patient-reported resolution of nausea, emesis, and abdominal pain should determine the timing of oral feeding reintiation.

Nonoral enteral feeding and parenteral feeding

Patients who cannot tolerate oral intake in 48 to 72 hours, especially those with severe AP and with ileus, require an alternate method of nutritional support. Total parenteral nutrition has been compared with enteral nutrition administered through a nasogastric (NG) or nasojejunal (NJ) tube in 12 RCTs.[60] The cumulative evidence from these RCTs

has suggested a lower length of stay, organ failure, and pancreatic infection among the NG/NJ compared with total parenteral nutrition group. Dysfunction of the gut barrier in the absence of enteral nutrition and transmigration of the gut flora has been suggested to increase the risk of infected pancreatic necrosis.[73] Based on this evidence, enteral nutrition is recommended even among patients with severe AP, through the NG/NJ if the oral route is not tolerated. Total parenteral nutrition or peripheral parenteral nutrition is not the preferred route for nutrition unless the enteral access is not available, is not tolerated (including trophic feeds), or is not able to meet adequate caloric requirements. Bakker and colleagues[74] compared NJ feed initiation in 24 hours with an oral diet after 72 hours with insertion of an NJ tube if not tolerated in an RCT of patients with predicted severe AP and demonstrated no difference in a composite outcome that included mortality or infectious complications.

Comparison of nasogastric or nasojejunal routes and formulations

NJ route was conventionally preferred over NG route to avoid the gastroduodenal phase of pancreatic stimulation. However, four RCTs have compared NJ and NG routes in patients with severe AP, in a meta-analysis[75] and have shown no difference in mortality, infectious complications, or length of hospital stay among the two groups. There were few reports suggesting reduced risk of aspiration pneumonitis in the NJ group but this was not conclusively demonstrated in the meta-analysis. The risk of pneumonitis is reduced by maintaining aspiration precautions, such as elevation of the head of the bed and monitoring for residuals in the stomach. NG tube placement is simpler, avoiding the need for endoscopic or interventional radiology services.

Role of Prophylactic Antibiotics in Acute Pancreatitis

AP, especially in moderate-severe form, is associated with local and systemic infectious complications. A recent systematic review has reported a two-fold increase in mortality in patients with infected pancreatic necrosis and organ failure (35.2%) when compared with sterile pancreatic necrosis and organ failure (19.8%).[76] SIRS caused by AP and nonpancreatic infections cannot be differentiated. Although antibiotics are clearly indicated in the setting of confirmed presence of infection, the use of antibiotics prophylactically in the setting of severe AP or sterile pancreatic necrosis to prevent infected pancreatic necrosis is controversial. Infected pancreatic necrosis was previously suspected to be a late complication of AP, but recent evidence has suggested otherwise, with nearly 50% of cases occurring within the first 7 days of hospitalization.[77] Multiple meta-analyses over the past few decades have provided contradictory recommendations regarding the use of prophylactic antibiotics in the setting of AP, because of underpowered RCTs lack of double blinding and with heterogeneity in patient population or antibiotic choice.[78] A recent Cochrane review[79] and an updated meta-analysis[60] summarized results from 10 RCTs and showed no mortality benefit or reduction in rate of infected pancreatic necrosis or persistent organ failure with the use of prophylactic antibiotics.

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