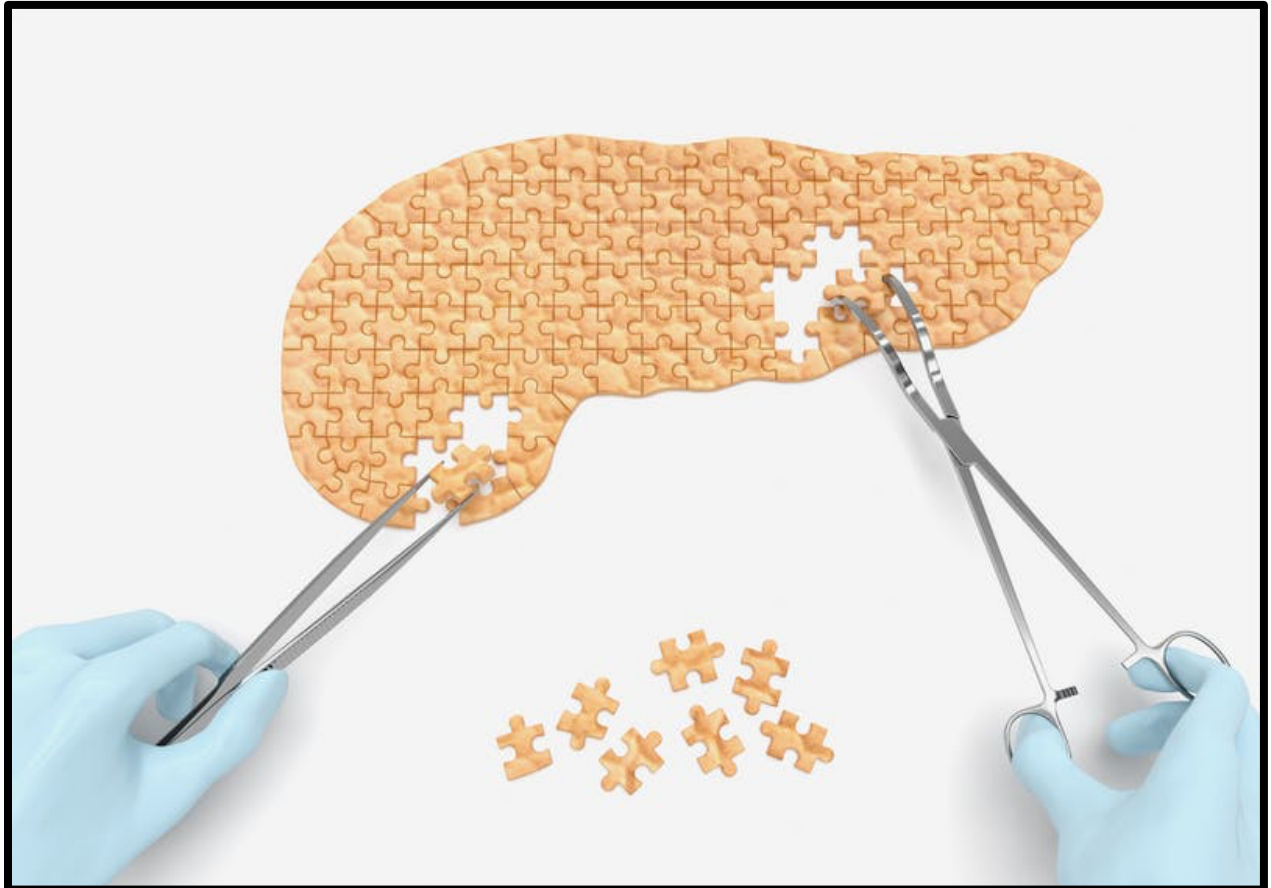


Acute Pancreatitis: Putting Together the Pieces of the Puzzle in 2018



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Department of Internal Medicine Grand Rounds

August 24, 2018

This is to acknowledge that Nisa Kubiliun, MD has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Kubiliun will not be discussing off-label uses in her presentation.

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Dr. Kubiliun received her medical degree from the University of Miami, Miller School of Medicine. She completed her Internal Medicine residency and also served as Chief Medical Resident at UT Southwestern Medical Center. She returned to Miami to complete her fellowship in Gastroenterology and pursued additional fellowship training in Interventional Gastroenterology at the University of Michigan. She currently serves as Clinical Chief of the Division of Digestive & Liver Diseases and directs the Pancreatic Cancer Prevention Program at UT Southwestern. She is also the director of endoscopy at Clements University Hospital and serves on the Training Committee for the American Society for Gastrointestinal Endoscopy.

Purpose and Overview

1. To provide an update on the most recent literature in the field of acute pancreatitis
2. To improve the clinical management of patients with acute pancreatitis
3. To discuss the role of interventional endoscopy in the management of pancreatitis related complications

Educational Objectives

At the end of this presentation, participants should be able to:

1. Define pancreatitis and describe its natural history
2. Describe the approach to management of acute pancreatitis
3. Identify patients at high risk for pancreatitis related complications

The Pancreas Throughout History

The initial anatomic descriptions of the pancreas date back to the third century BCE when Herophilus, regarded as the father of anatomy, provided the first anatomical description of the organ. Four hundred years later, Ruphos of Ephesus named the pancreas. The pancreas was regarded as unusual given that it had no cartilage or bone. This led to its name (pan - all, kreas - flesh or meat). It was not until 1642 when a detailed anatomic description of the pancreas by Wirsung first emerged. Wirsung's discovery of the main and accessory pancreatic ducts definitively established the role of the pancreas as a secretory gland. This discovery abolished the previous theory that the pancreas acted as a cushion for the stomach and led directly to studies of the physiology of the gastrointestinal tract. Ten years later, the first clinical description of acute pancreatitis is believed to have been published.¹

Epidemiology

Acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract, leading to significant morbidity, mortality and financial burden. In 2009, AP was the most common gastroenterology discharge diagnosis with a cost of 2.6 billion dollars.

The number of discharges with a primary inpatient diagnosis of AP in the United States has more than doubled from 1983 to 2010. In 2010, there were 275,000 admissions for AP in the US compared to ~100,000 admissions in 1983.²

Defining Pancreatitis

Initial attempts to streamline the definition of pancreatitis and to develop a standardized classification system of severity began with the Atlanta Symposium in 1992.³ Although this was hailed as a major accomplishment in the field, many of the definitions proved confusing and tools to aid clinical assessment of severity were lacking. Better understanding of the pathophysiology of organ failure and necrotizing pancreatitis, as well as improved diagnostic imaging, served as an impetus to revise the Atlanta Classification. The revised Atlanta Classification, published in 2012, provides criteria for the diagnosis of AP, differentiates the two types of AP (interstitial edematous pancreatitis and necrotizing pancreatitis), classifies the severity of AP into three categories, and formally establishes definitions for the local complications which can arise in the setting of AP.⁴

The diagnosis of AP requires two of the following three features: (1) abdominal pain consistent with AP (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum lipase activity (or amylase activity) at least greater than three times the upper limit of normal; and (3) characteristic findings of AP on contrast-enhanced computed tomography, magnetic resonance imaging, or transabdominal ultrasonography.⁴

Etiology of Pancreatitis

Biliary Pancreatitis

The list of potential causes of AP is long and complex. In most series, gallstones continue to be one of the two leading causes of AP.⁵ Identification of gallstones or biliary sludge in an individual without another potential etiology should prompt referral for cholecystectomy to prevent recurrent attacks. The mechanism via which gallstones lead to biliary pancreatitis will be covered later in the protocol.

Alcohol

Alcohol is responsible for ~40% of all episodes of AP. Prolonged overconsumption of alcohol typically precedes the initial attack of acute alcoholic pancreatitis, whereas isolated alcohol binges rarely cause pancreatitis. In fact, the incidence of pancreatitis in alcoholics is surprisingly low (5/100,000), indicating that in addition to the quantity of alcohol ingested, specific susceptibility factors such as cigarette smoking or underlying genetic predisposition may play a role.⁵ The identification of these susceptibility factors remains a critical area of investigation.

Drug Induced Pancreatitis (DIP)

In the absence of gallstones or alcohol, there are specific factors which must be considered and systematically examined. For example, a complete review of a patient's medication history is critical in the evaluation of AP. DIP is assumed to be a relatively rare entity, with an incidence reported between 0.1 and 2% of AP cases.⁶ However, in the absence of clinical trial data, a standardized definition of DIP, and a lack of reliable reporting, the true incidence of DIP is unknown and is likely significantly higher than what is currently reported in the literature.

Five hundred and twenty-five different drugs suspected to cause AP are reported in the database of the World Health Organization (WHO). The ability to establish causality for many of these drugs remains elusive and for only a small portion of these drugs has definite causality been established.⁷

Some of the most commonly prescribed medications in the United States have been associated with AP. For example, in one case-control study, the use of ACE inhibitors was associated with an increased risk of AP, with an odds ratio of 1.5. The risk increased with higher daily doses and was highest during the first 6 months of therapy. Pancreatitis associated with ACE inhibitors is thought to reflect localized angioedema of the gland, potentially related to decreased bradykinin degradation.⁸ A similar class effect has been described with statin medications. Although the mechanism of action remains unclear, DIP has been documented in case reports involving atorvastatin, fluvastatin, rosuvastatin, simvastatin, and pravastatin. Statin-induced pancreatitis seems to be very uncommon early in treatment and more likely to occur after prolonged use.⁸

Infectious Pancreatitis

A significant number of cases of AP can be attributed to various classes of infectious organisms including viruses, bacteria, fungi, and parasites. The greatest number of infectious cases of pancreatitis are caused by viruses including Hepatitis B, Coxsackie virus, CMV, HIV, HSV, mumps, and varicella-zoster virus.⁹ Bacterial pathogens have also been associated with AP in numerous studies. The most commonly implicated organisms include *Mycoplasma pneumoniae* and *Salmonella paratyphi*. AP associated with other organisms including *Campylobacter jejuni*, *Yersinia enterocolitica*, *Yersinia pseudotuberculosis*, *Brucella*, and *Nocardia* has been reported in the literature. Pancreatitis caused by parasitic infections has been well described and in many cases the mechanism has been clearly elucidated. *Ascaris lumbricoides* is the most common parasite implicated in AP. The mechanism of pancreatitis involves obstruction of the pancreatic duct by the adult worm, which has been observed radiographically as well as endoscopically. Lastly, fungal organisms have been associated with

AP despite a lack of clear evidence in the literature. The two most commonly named fungi are *Aspergillus* and *Candida*.

Malignancy

The importance of considering pancreatic tumors as causative agents in the development of AP cannot be overstated. A retrospective review published in 2013 set out to examine the frequency of pancreatic cancer presenting as AP. The authors eliminated all patients in whom pancreatitis could be attributed to either alcohol or biliary tract disease. They then examined the charts of 332 patients who presented for endoscopic ultrasound after an episode of unexplained pancreatitis. A startling 17% of individuals presenting with unexplained AP had a newly identified adenocarcinoma and 3.2% of patients were found to have an underlying IPMN (a premalignant cystic lesion of the pancreas).¹⁰

These statistics argue for a strong association between pancreatic cancer and pancreatitis and highlight the need for a high index of suspicion for underlying malignancy when other causes of pancreatitis are excluded.

Hypertriglyceridemia

Metabolic factors such as hypertriglyceridemia can precipitate episodes of AP. Hypertriglyceridemia induced pancreatitis is responsible for 1 to 14 percent of all cases of AP and is one of the most common etiologies of pancreatitis during pregnancy.^{11,12} The risk of developing pancreatitis increases in proportion to the degree of triglyceride elevation – the risk of developing pancreatitis in patients with serum triglycerides >1000 mg/dL and >2000 mg/dL is ~5% and 10%-20%, respectively.¹¹ Additionally, the degree of triglyceride elevation is felt to be directly related to the severity of AP.¹³ In most cases of triglyceride induced pancreatitis serum triglycerides are > 1000mg/dL. This occurs most commonly in individuals with familial hypertriglyceridemia, uncontrolled diabetes mellitus, and during pregnancy. Although the precise mechanism of triglyceride induced pancreatitis is unknown, it is felt that when lipase, which is continuously released from the pancreas, is exposed to circulating triglyceride, hydrolysis of the triglyceride into short-chain fatty acids occurs which can be toxic to the pancreas and cause ongoing inflammation.

Autoimmune Pancreatitis

Autoimmune pancreatitis is the pancreatic manifestation of a systemic inflammatory disorder mediated by infiltration of IgG4 positive plasma cells. IgG4 related disease has been described in virtually every organ system, including the biliary tree, salivary glands, kidneys and lymph nodes. The "HISORT" criteria, proposed by the Mayo Clinic, are the most commonly used diagnostic criteria in the United States and include the presence of one or more of the following: diagnostic histology, characteristic imaging on computed tomography (CT) and/or pancreatography, elevated serum IgG4 levels on serologic testing, other organ involvement and a response of pancreatic and extrapancreatic manifestations to glucocorticoid therapy.¹⁴

The Role of Genetic Mutations

Certain genetic mutations have been associated with acute (and ultimately chronic) pancreatitis and center around the role of trypsin activity. Trypsin is primarily responsible for the activation of pancreatic zymogens into pancreatic digestive enzymes after they are

secreted into the duodenum. When digestive enzymes are prematurely activated in the pancreas, pancreatic injury and immune system activation ensue, leading to AP and later chronic pancreatitis. Mutations in the serine protease 1 gene (PRSS1), lead to premature activation of trypsinogen to trypsin and are responsible for autosomal dominant hereditary pancreatitis. Mutations in pancreatitis susceptibility genes such as SPINK1, CTSC, and CFTR impair trypsin metabolism and can impair the destruction, inhibition or elimination of trypsin from the pancreas, leading to pancreatitis.

Idiopathic Pancreatitis

Idiopathic pancreatitis is defined as pancreatitis for which no etiology is identified after initial laboratory and imaging studies. Anatomic abnormalities such as pancreas divisum (PD) have been evaluated as a potential cause of idiopathic pancreatitis. PD is an embryologic abnormality in which the dorsal and ventral pancreatic ducts fail to fuse during development. It is the most common pancreatic congenital anomaly and has been described in approximately 7% of autopsy series. The classic PD anatomy consists of a small ventral duct, which drains through the larger major papilla, and the larger dorsal duct, which drains through the smaller minor papilla (see figure below). Most individuals with PD are asymptomatic, but there exists a subset of patients who experience episodes of acute recurrent pancreatitis in the setting of PD. The pathophysiology is felt to be related to excessively high intrapancreatic dorsal ductal pressure across a tiny minor papilla, which may result in inadequate drainage and ductal distension. Studies suggest that PD by itself is not a cause of pancreatitis, rather that most symptomatic patients also carry an underlying genetic mutation in the CFTR gene, suggesting a cumulative effect of these two factors.¹⁵

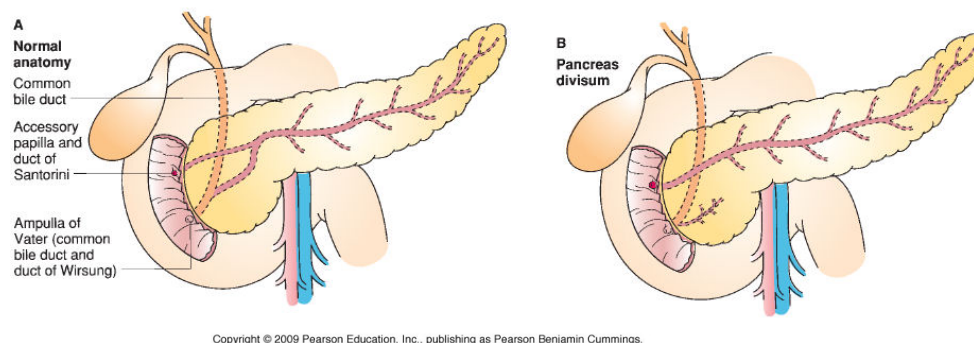


Figure 1. A. Normal pancreatic anatomy with the duct of Wirsung (ventral duct) draining the majority of the gland via the major papilla. B. Pancreas divisum anatomy with the dorsal duct draining the majority of the gland via the minor papilla.

Grading of Severity

There are three critical factors in determining the severity of an episode of pancreatitis. The presence of:

1. local complications: acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis
2. systemic complications: exacerbations of underlying co-morbidities related to the acute pancreatitis (coronary artery disease, underlying pulmonary disease)

3. organ failure: (renal, cardiovascular, respiratory), defined as transient (<48 h) vs. persistent organ failure (>48 h)

Severity can be classified as mild, moderately severe, or severe.

1. Mild: no organ failure, local or systemic complications. Typically, mild pancreatitis resolves in the first week and mortality is very rare.
2. Moderately severe: transient organ failure, local complications or exacerbation of co-morbid disease. Mortality in moderately severe pancreatitis is estimated between 1-8%.
3. Severe: persistent organ failure lasting >48 h. In severe pancreatitis mortality can be as high as 36-50%.

From a clinical perspective, this classification system does little at the time of presentation to aid in predicting how severe an episode of pancreatitis will be. Countless predictive scoring systems such as Ranson's, Acute Physiology and Chronic Health Evaluation II (APACHE-II) and Glasgow have historically been used to predict severity. These systems are significantly limited by their cumbersome design (require multiple variables) and require a full 48 hours to complete. The ideal mortality prediction tool would require only a small number of easily accessible variables and be readily applied at the time of admission; therefore, it could serve as a tool to triage patients to the appropriate level of care. Early risk stratification can also help identify patients who are more likely to suffer complications such as organ failure or infected necrosis, allowing for more aggressive resuscitation in the early hours after presentation.

In 2008, Wu et al introduced the Bedside Index for Severity in Acute Pancreatitis (BISAP) tool, with the goal of creating a simple and accurate clinical scoring system that could be used at the time of presentation to predict mortality.¹⁶ The authors examined data collected within the first 24 hours of hospitalization from 17,992 cases of AP. They identified 5 variables to aid in predicting in-hospital mortality, which included: BUN>25, impaired mental status, greater than or equal to 2 systemic inflammatory response syndrome (SIRS) criteria, age >60, and the presence of a pleural effusion. Each variable is weighted equally and assigned one point if present. Mortality ranged from >20% in the highest risk group to <1% in the lowest risk group. Those patients with a score of three or more had significantly increased mortality rates (score 2 = 2.1% observed mortality, score 3 = 8.3% observed mortality, score 4 = 19.3%, score 5 = 26.7%). Since inception, the BISAP tool has been compared to the more cumbersome scoring systems and it performs similarly, with the advantage that providers can complete it at the bedside at the time of presentation to aid in the early identification of patients at increased risk for in-hospital mortality.¹⁷

Types of Acute Pancreatitis and Local Complications

AP can be subdivided into two broad types: interstitial edematous pancreatitis and necrotizing pancreatitis, which have very different clinical outcomes. Edematous pancreatitis is characterized on CT by normal parenchymal enhancement with minimal heterogeneity, reflecting edema within the gland. The peripancreatic tissues may reveal stranding within the peripancreatic fat with varying amounts of peripancreatic fluid. In the acute setting (<4 weeks), these fluid collections are referred to as acute peripancreatic fluid collections (APFCs) and are exclusively comprised of a liquid component without any solid debris. APFCs lack a well-defined wall and are often the result of leakage of pancreatic enzymes from a ruptured side-branch duct. The majority of APFCs resolve spontaneously within the first few weeks after an

episode of AP. If an APFC persists beyond 4 weeks, as is seen in 10–20% of patients, it is likely to turn into a pseudocyst. Pseudocysts are well-defined fluid collections in the peripancreatic space which lack a solid component. Fluid analysis reveals amylase and lipase rich fluid consistent with the thinking that pseudocysts arise from disruption of the pancreatic ductular system, with persistent leakage of pancreatic juice into the collection.

Edematous pancreatitis represents ~80% of all episodes of pancreatitis and has an associated mortality rate of <1%. In sharp contrast, necrotizing pancreatitis comprises the remaining 20% of pancreatitis cases and has an associated mortality of 10% in the setting of sterile necrosis, and a startling ~40% mortality in the setting of infected necrosis.⁴

Necrotizing pancreatitis occurs as a consequence of impaired pancreatic perfusion and is characterized by non-enhancement of the pancreatic parenchyma on contrast enhanced CT scan. During the first four weeks of an episode of necrotizing pancreatitis, individuals may develop an acute necrotic collection (ANC), characterized by variable amounts of fluid and necrotic tissue as the composition of the collection changes with ongoing liquefaction of necrotic material. These collections can involve the pancreatic parenchyma and/or the peripancreatic tissues and are at risk of infection. Approximately 4 weeks after an episode of necrotizing pancreatitis, if an ANC is not resorbed, the necrosis can mature and evolve into an encapsulated collection with a well-defined inflammatory wall. This is referred to as walled off pancreatic necrosis (WOPN) and is also at risk of infection. Infected necrosis should be suspected in the setting of clinical deterioration, and the diagnosis can be presumed when there is gas identified within the necrotic collections or extraluminal gas bubbles identified on imaging. Establishing a timely diagnosis of infected pancreatic necrosis is critical to the initiation of antibiotic therapy and to guide the need for percutaneous, endoscopic or surgical intervention.

Treatment of Acute Pancreatitis

Fluid Resuscitation in Acute Pancreatitis

The role of intravenous fluids in the management of AP has been the source of great debate for many decades. In order to understand the role of IVFs in the treatment of AP, we first need to review the physiology of AP. As the inflammatory process progresses in AP, there is extravasation of protein-rich intravascular fluid into the peritoneal cavity resulting in decreased intravascular volume and hemoconcentration which is reflected by rising hematocrit and BUN. Decreased intravascular volume leads to a decrease in pancreatic blood flow and decreased perfusion to the pancreas, which can lead to pancreatic necrosis. A vicious cycle develops where pancreatic inflammation leads to more third spacing into the peritoneum leading to more necrosis. Often this is profound, as described by Greer and Burchard, “inflammation begets hypoperfusion and hypoperfusion begets inflammation,” leading to a self-propagating cycle that causes vascular dysfunction in both large vessels as well as the microcirculation of the pancreas.¹⁸

The only way to halt this cycle is to provide vigorous intravenous hydration leading to intravascular volume repletion, and thereby increasing pancreatic perfusion. Fluid resuscitation is a cornerstone in the treatment of AP during the first 24 hours, and under-resuscitation is

associated with increased morbidity (including the development of SIRS, necrotizing pancreatitis, and organ failure) and mortality.^{19,20}

When considering IVF resuscitation, the most critical questions center around the optimal infusion rate and volume, the type of fluid for initial resuscitation, and measures to assess whether appropriate fluid resuscitation has been achieved. There is currently a paucity of human randomized controlled trials, and nearly all current guidelines for resuscitation are vague and based almost exclusively on expert opinion.

Type of Fluid for Initial Resuscitation

The first decision in initiating IVF therapy is determining which fluid to give. Infusion of large volumes of normal saline (NS) can lead to development of a hyperchloremic metabolic acidosis, thereby worsening pancreatitis. In a well-designed prospective randomized trial, hydration with a lactated ringer's (LR) solution resulted in fewer patients developing SIRS as compared with patients receiving normal saline (84% reduction vs 0%, respectively; $P=.035$). Administration of LR also reduced levels of CRP, compared with NS (51.5 vs 104 mg/dL, respectively; $P=.02$).²¹ There has since been a second randomized controlled trial published this year, with an additional 40 patients randomized to NS vs LR, and these results have been reproduced.²² These trials have made their way into national guidelines but it is critical to note that these studies did not examine clinical outcomes such as organ failure, ICU stay, pancreatic necrosis, pancreatic infection, length of hospital stay or in hospital mortality. Moreover, this data is based on a grand total of two RCTs comprised of eighty total patients. Despite this limited data, in 2018, most guidelines support resuscitation with LR over NS in AP.^{23,24}

Optimal Infusion Rate and Volume

It is now widely accepted that resuscitative efforts should begin as early as possible in the course of AP. But is there data to guide whether an optimal IVF infusion rate and amount of fluid exists? The rate of fluid resuscitation has generally been divided into "aggressive" and "non-aggressive" categories. Although the definition of "aggressive" has not been uniformly defined in the literature, across studies the median volume given in the aggressive treatment groups was 4.5L in the first 24 hours (range 3.5-5.4L), while the median volume in the non-aggressive groups was 3.5L in the first 24 hours (range 1.7-4L). Eleven studies of generally poor quality using heterogeneous goals and protocols have aimed to shed light on this critical topic. Of the eleven studies, nine^{19,20,25-31} are observational and only two are RCTs.^{32,33} The results of these studies are mixed, with four studies (all observational) providing evidence in favor of aggressive fluid resuscitation.^{19,20,25,28} The remaining seven studies suggest a benefit to a non-aggressive fluid resuscitation strategy.^{26,27,29-33} Unfortunately, in the absence of clear definitions as to what constitutes aggressive vs. non-aggressive volume resuscitation, it is important to cautiously interpret the data. Moreover, these studies are also limited by a serious risk of selection bias and methodological design flaws. For example, it is certainly plausible that sicker patients were triaged to receive faster rates of IVFs to support hemodynamics, rather than aggressive IVFs being responsible for clinical deterioration. In the absence of high quality RCT data the jury is still out as to which resuscitation strategy is best.

A summary of the most recent recommendations for the management of fluid resuscitation in AP from recent national guidelines is highlighted in Table 1.

Author	Journal	Initial Resuscitation Recommendation
Tenner et al. ²³	Am J Gastroenterol, 2013	Aggressive hydration (250–500 mL/h). Bolus administration for severe volume depletion. Lactated Ringers preferred. Target fluid resuscitation to BUN. Assess fluid requirements within 6 h of admission, and for next 24–48 h.
Crockett et al. ³⁴	Gastroenterology, 2018	Goal-directed therapy for fluid management. No recommendation whether normal saline or Ringer's lactate is used.
Arvanitakis et al. ²⁴	Endoscopy, 2018	Initial goal-directed intravenous fluid therapy with Ringer's lactate (e. g. 5 - 10 mL/kg/h) at onset. Fluid requirements should be patient-tailored and reassessed at frequent intervals.

Table 1. Most recent guidelines for fluid resuscitation in acute pancreatitis.

Markers to Assess Adequate Resuscitation

Another aspect of IVF resuscitation in AP is the identification of markers to assess whether appropriate fluid resuscitation has been achieved. There are several studies evaluating a variety of resuscitation goals from bedside assessments to laboratory based tests, but there is no clear consensus on which marker is best. A total of six studies have investigated the role of goal directed therapy – with metrics such as heart rate, blood pressure, mean arterial pressure, urine output, HCT, BUN, creatinine, central venous pressure, stroke volume variation, and intrathoracic blood volume.^{25,32,35-38}

In a large retrospective cohort study of patients with AP, both the initial BUN level and subsequent change in BUN level during the initial 24 hours of hospitalization were independent predictors of mortality.³⁶ The accuracy of measuring serial BUN levels has been validated using data from three independent prospective cohort studies. Among patients with an elevated BUN value at admission (>20 mg/dL), a decrease of at least 5 mg/dL at 24 hours was associated with reduced risk of in-hospital death. In contrast, among patients with a normal BUN value at admission, even the slightest rise in BUN level (≥ 2 mg/dL) was associated with an increased risk of mortality.³⁹

Based on this data, the same authors hypothesized that a goal-directed approach to early fluid resuscitation based on changes in BUN level and serial bedside exams would provide a safer, more objective approach to fluid replacement compared with conventional fluid resuscitation.²¹ They designed a study to test this hypothesis, in which the primary study outcome was systemic inflammation, measured clinically as the change in prevalence of SIRS at 24 hours post-randomization. The authors concluded that goal-directed resuscitation did not significantly

reduce the incidence of SIRS (11.8% vs 13.0%, respectively; $p = .85$), or levels of CRP after 24 hours (87.1 vs 69.2 mg/dL, respectively; $p = .75$) compared with standard resuscitation.

The concept of early goal directed fluid therapy can be found throughout the AP literature but the data “remains paltry and of poor quality”.⁴⁰ The application of goal directed therapy to the management of AP is in its infancy and lacks a clear role or definition. Future studies should be designed to identify the parameters with the most meaningful clinical impact. The following point cannot be over emphasized -- in 2018 there are a lack of rigorously designed RCTs to guide the management of AP as it pertains to IVF hydration. Clinical practice is dictated by national guidelines which are largely based on expert opinion. The field is ripe for clinical trials designed to address multiple important but unanswered questions, including the ideal volume and rate of fluid therapy, the role of goal-directed therapy, and the optimal duration of fluid resuscitation. It is critical that fluid requirements be reassessed at frequent intervals within six hours of admission and for the next 24–48 hours with careful attention to clinical parameters such as urinary output, heart rate, blood pressure and abdominal exam. It may also be reasonable to aim at decreasing BUN, but reliance upon laboratory parameters alone is insufficient to guide resuscitation strategies.

Pancreatic Infections and the Role of Prophylactic Antibiotics

The early phase of pancreatitis (first 1-2 weeks) is dictated by the body's response to pancreatic injury. A pro-inflammatory response develops, which results in SIRS. It is also during this time (usually within the first 4 days) that pancreatic necrosis can develop. Notably, sepsis or infection rarely develops during the early phase. If the SIRS response is severe and persistent it can progress to multi-organ failure. After the first 1-2 weeks, a transition from a pro-inflammatory to an anti-inflammatory response occurs. The patient is then at risk for translocation of intestinal flora due to breakdown of the intestinal barrier and subsequent development of secondary infection of the necrotic tissue and fluid collections. The organisms responsible for infection of pancreatic necrosis are predominantly gut-derived, including *Escherichia coli*, *Pseudomonas*, *Klebsiella*, and *Enterococcus*. Fungal infection and infection with gram-positive organisms are uncommon but occur more frequently in the setting of prophylactic antibiotic use for severe AP, especially when used for more than 10–14 days.⁴¹ The role of antibiotics in the prevention of infection has been studied extensively. All consensus guidelines published by the major gastroenterology societies are clear in their recommendations: “Intravenous antibiotic prophylaxis is not recommended for the prevention of infectious complications in AP, severe AP, or necrotizing pancreatitis.”^{23,42} This recommendation is based in part on a randomized, multicenter, prospective, double-blind, placebo-controlled study.⁴³ One hundred patients with severe necrotizing pancreatitis were randomized to meropenem or placebo. Pancreatic or peripancreatic infection developed in 18% of patients in the group treated with meropenem, compared with 12% of patients taking placebo ($P = 0.401$). The overall mortality rate was 20% in the meropenem group and 18% in the placebo group ($P = 0.799$).

The largest and most recent systematic review/meta-analysis evaluating the role of prophylactic antibiotics in severe AP was published in 2011. The authors analyzed fourteen trials with a total of 841 patients. The results were mixed, with a trend favoring the use of antibiotics, but did not achieve statistical significance in preventing infection or mortality.⁴⁴

Generally, at the time of initial presentation, the risk of infected pancreatic necrosis is low. There is no data to support prophylactic antibiotic use in this setting to prevent infected necrosis. At the time of presentation, antibiotics are indicated when there is proven extra-pancreatic infection, such as cholangitis, urinary tract infection or pneumonia. As previously mentioned, infected necrosis should be considered in patients who deteriorate or fail to improve after a week of treatment. Clinical signs (persistent fever, tachycardia, worsening leukocytosis) and imaging signs (appearance of gas within the collections) are accurate predictors of infected necrosis and should prompt immediate initiation of antibiotics. In cases of suspected infected necrosis, antibiotic therapy should be initiated while the patient undergoes workup for infected necrosis. Imipenem or meropenem have historically been the agents of choice for patients with suspected infected necrosis based on their high pancreatic tissue levels and bactericidal activity against most of the organisms present in pancreatic infection. In an effort to preserve the use of carbapenems at our institution, recommendations for antibiotic management of abdominal sepsis with suspected pancreatic involvement include piperacillin-tazobactam or cefepime plus metronidazole.

Nutrition in Pancreatitis

Alimentation in pancreatitis remains a controversial topic with two critical questions at the center of the debate: 1) What is the preferred route of nutrition – total parental nutrition (TPN), nasogastric (NG) feeding, nasojejunal (NJ) feeding, or even oral feeding? 2) When in the course of an episode of AP should feeding begin?

Parenteral vs. Enteral Feeding

Prolonged parenteral feeding carries numerous unfavorable side effects such as catheter related infections, gut atrophy and increased gut permeability. The lack of peristaltic stimulation results in hypomotility of the gut. The only major postulated benefit of TPN is the lack of pancreatic stimulation achieved by avoiding feeding into the gut.

Conversely, enteral feeding maintains gut integrity, facilitates gut motility which protects against the overgrowth of abnormal intestinal flora, and increases gut permeability therefore preventing bacterial translocation. One potential downside to enteral feeding is that it may lead to pancreatic stimulation, causing additional pain and intolerance of enteral nutrition. A number of RCTs and subsequent meta-analyses conducted in patients with moderate to severe AP have demonstrated that enteral nutrition, when compared to parenteral nutrition, is able to reduce pancreatic and extrapancreatic infective complications, multi-organ failure, surgical intervention, and mortality.⁴⁵ Parenteral nutrition should therefore be avoided unless the enteral route is not available or not tolerated.

Nasogastric vs. Nasojejunal Feeding

Traditionally, it was believed that stimulation of pancreatic secretion by feeding into the proximal GI tract with oral or NG feeding was detrimental, but data in recent years suggests that this is less of a clinically significant concern. In 2005, an RCT comparing early NG versus NJ feeding was performed.⁴⁶ The study randomized 50 patients to either NG or NJ feedings and looked at APACHE 2 scores, CRP, and pain as their primary outcomes. There was no significant difference in any of the endpoints between the NG group and the NJ group. Since this study was published in 2005, a number of trials and a meta-analysis comparing NG versus NJ feeding in severe AP have demonstrated similar outcomes, with no statistical difference in

terms of mortality, tracheal aspiration, diarrhea, exacerbation of pain and delivery of adequate nutrition.^{47,48} Practical factors frequently serve to guide the decision between NG vs NJ feeding. Gastric feeding is easy to initiate as NG tube placement can be performed at the bedside, therefore facilitating early enteral nutrition. In contrast, NJ tube placement requires involvement from gastroenterology or radiology, potentially delaying time to initiating nutrition. It is also important to consider that certain conditions specific to AP may prevent the use of NG feeding – for example, gastric outlet obstruction secondary to pancreatic inflammation or a pancreatic fluid collection causing duodenal compression.

When to Begin Feeding

The question of when to initiate feeding in the setting of AP has been the source of much investigation. In the past, it was accepted practice that bowel rest would limit the degree of inflammation associated with pancreatitis by decreasing pancreatic secretion. Numerous RCTs have dispelled this hypothesis and have shown a benefit to early oral/enteral feeding. These studies have shown that nasoenteric tube feeding started within 48 hours after admission, as compared with a start after 48 hours, significantly reduced the rate of major infection and in some studies even reduced mortality.⁴⁹⁻⁵¹

Biliary Pancreatitis

The precise mechanism of acute biliary pancreatitis remains unclear. A link between gallbladder stones and pancreatitis has been suspected since at least the 17th century but precisely how gallstones are responsible for pancreatitis has been the matter of much debate. Biliary pancreatitis is felt to occur when a gallstone leaves the gallbladder, traverses the cystic duct, travels down the common bile duct and becomes lodged within the common channel shared by the pancreas and bile duct (Figure 2). This process may result in obstruction of the pancreatic duct, leading to ductal hypertension and subsequent unregulated activation of trypsin, a known mechanism for inducing pancreatitis. Even the presence of sludge or microlithiasis, without overt obstruction, can induce transient spasm or local edema at the ampulla resulting in temporary obstruction.⁵²

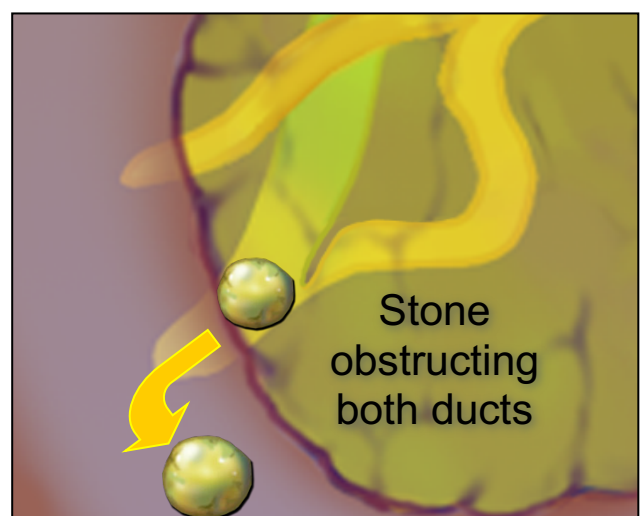
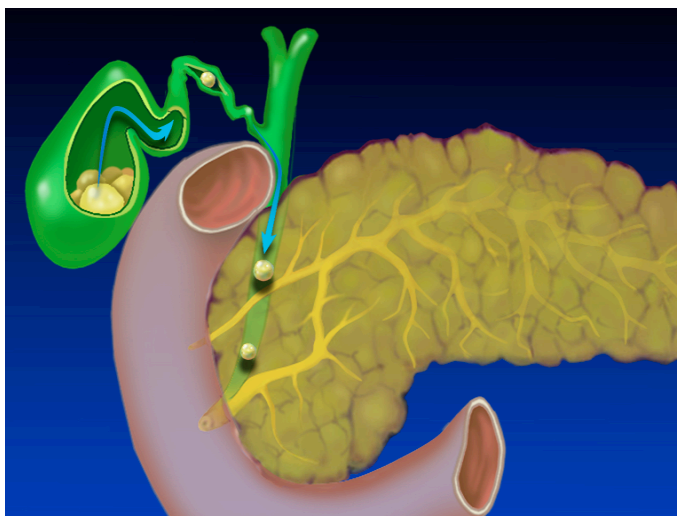


Figure 2. Pathogenesis of biliary pancreatitis.

Establishing the diagnosis of biliary pancreatitis can be challenging. Suspicion for a biliary tract cause is supported in the presence of a three-fold elevation of ALT, which has a positive predictive value of 96%.⁵³ Unfortunately, the sensitivity of this single parameter is only 48%; therefore, a normal ALT cannot be relied upon solely to exclude gallstones as a cause.

In order to correctly establish this diagnosis, an understanding of the anatomic relationship between the pancreas and the biliary tree is paramount. The distal bile duct courses through the head of the pancreas. Pancreatic head edema in the setting of pancreatitis from any cause may result in compression of the distal bile duct leading to transient stasis or obstruction. This process can produce laboratory findings similar to those seen in biliary pancreatitis. Therefore, liver enzyme elevation at the time of presentation may not necessarily be diagnostic of a biliary etiology. Irrespective of the etiology, as pancreatic inflammation improves, so should the degree of liver enzyme elevation. Improving pancreatitis with persistently elevated liver chemistries should prompt suspicion for ongoing biliary obstruction.

Fortunately, most cases of biliary pancreatitis are caused by small stones (microlithiasis <5mm), which spontaneously migrate across the ampulla, pass into the duodenum, and are excreted in the stool. However, in some patients, choledocholithiasis can lead to ongoing biliary and/or pancreatic duct obstruction, resulting in cholangitis or worsening pancreatitis. Numerous clinical trials have been conducted to evaluate the role of early ERCP in the setting of AP.⁵⁴⁻⁵⁸ The two critical questions related to the role of ERCP in biliary pancreatitis are: 1) Does early ERCP mitigate the severity of pancreatitis? and 2) Is there a benefit to those patients without biliary obstruction or cholangitis? Many RCTs to date have included patients with evidence of ongoing obstruction and clinical cholangitis, making interpretation of the data challenging – as these patients would clearly be expected to benefit from early ERCP.

In an attempt to evaluate the role of ERCP in patients without cholangitis or biliary obstruction, Folsch et al. conducted a multicenter study of ERCP in acute biliary pancreatitis which excluded patients with a bilirubin > 5 mg/dl.⁵⁵ These criteria relegated patients with cholangitis and/or biliary obstruction to early ERCP, and they were not included in this study. No benefit in morbidity and/or mortality was seen in the remaining patients who underwent early ERCP. The findings of this study reinforce the concept that the benefit of early ERCP is seen in patients with AP complicated by cholangitis or biliary obstruction, but not severe AP alone. Numerous guidelines and meta-analysis recommend against the routine use of early ERCP for all patients with acute biliary pancreatitis.^{59,60} The need and urgency of ERCP should be based on the degree of concern for the presence of cholangitis or biliary obstruction, the clinical condition of the patient, and response to initial conservative management.

Management of Local Complications

As previously reviewed, in the acute setting, edematous pancreatitis can result in inflammatory APFCs. If an APFC persists beyond 4 weeks, it is likely to turn into a pseudocyst. Historically, the teaching has been that pseudocysts of more than 6 cm in diameter which have been present for 6 weeks require intervention. It is now widely recognized that most pseudocysts regress spontaneously over time and require no treatment. Indications for drainage include the presence of symptoms related to compression of surrounding structures (e.g. gastric outlet obstruction), enlargement of the cyst, or complications including infection and hemorrhage. In

light of significant overlap in the management of pseudocysts and walled off necrosis, drainage options for both will be discussed below.

Akin to the APFC in the setting of edematous pancreatitis, ANC may occur in the setting of necrotizing pancreatitis. If we look at infected pancreatic necrosis in particular, historically, patients with infected pancreatic necrosis were treated via open surgical debridement to completely remove the infected necrotic tissue. This was a highly invasive procedure associated with high rates of complications (34 to 95%) and death (11 to 39%) and with a risk of long-term pancreatic insufficiency, not to mention frequently requiring multiple trips to the operating room for subsequent debridement. Over the years, the management of infected necrosis has been modified in several ways. First, it is now known that waiting 3–4 weeks after the onset of pancreatitis is associated with decreased complications as this allows for the encapsulation of ANCs into WOPN, which will improve conditions for intervention. Over time, less invasive routes for debridement were developed, including percutaneous drainage (PCD), endoscopic (transgastric) drainage, and a procedure known as minimally invasive retroperitoneal necrosectomy. These techniques can be performed independently or in a so-called step-up approach.

The step-up approach aims at controlling the source of infection, rather than complete removal of the infected necrotic tissue. The first step is percutaneous drainage of the collection of infected fluid to mitigate sepsis. This step may postpone or even eliminate the need for surgical necrosectomy. PCD drainage is performed by interventional radiology, typically under CT guidance. Pigtail catheters of varying diameter can be advanced into the collection under radiographic visualization and attached to a drainage bag. The catheter allows for frequent irrigation of the cavity, which aids in mechanical debridement of the contents. Repeat imaging is typically performed a few weeks after catheter placement to assess for resolution of the collection. Unfortunately, only ~50% of all patients treated with PCD as monotherapy achieve resolution and can avoid additional intervention.

When percutaneous monotherapy fails, the next step is minimally invasive retroperitoneal necrosectomy. A subcostal incision is made and the percutaneous drain is followed into the collection. First necrosis is removed under direct vision, followed by further debridement under videoscopic assistance – see Figure 3.

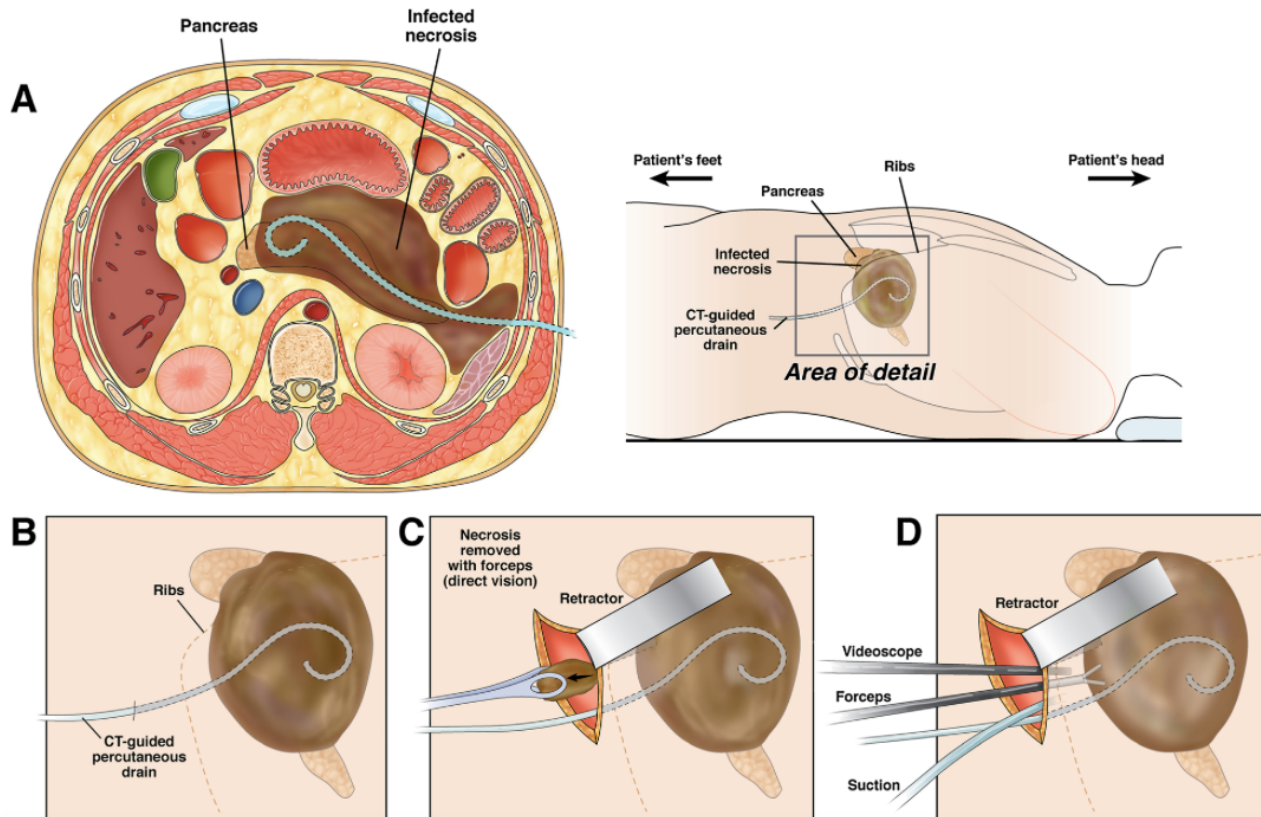


Figure 3. Step up approach to the management of pancreatic necrosis.

This step-up approach was compared head-to-head with open necrosectomy in a pivotal NEJM article published in 2010.⁶¹ Eighty-eight patients with necrotizing pancreatitis and suspected or confirmed infected necrotic tissue were randomly assigned to undergo primary open necrosectomy or a step-up approach to treatment. The primary end point was a composite of major complications or death. The primary end point occurred in 69% of patients assigned to open necrosectomy and in 40% assigned to the step-up approach $P=0.006$. New-onset multi organ failure occurred less often in patients assigned to the step-up approach than in those assigned to open necrosectomy (12% vs. 40%, $P=0.002$). Despite significant improvement in outcomes with the step-up approach when compared to open necrosectomy, the procedure remains morbid. The proximity of the stomach and duodenum to the peripancreatic space, coupled with advances in flexible endoscopy and endoscopic ultrasonography over the past decade, has set the stage for a potentially even less invasive alternative – endoscopic pancreatic access and necrosectomy. Earlier this year, a landmark RCT published in the Lancet compared endoscopic therapy to a surgical step up approach for infected pancreatic necrosis.⁶² In the surgical group, patients underwent catheter drainage followed, if needed, by “minimally invasive” necrosectomy, whereas the endoscopic step-up approach consisted of endoscopic transluminal drainage followed by endoscopic necrosectomy if needed. Ninety-eight patients were enrolled. The primary endpoint was a composite of major complications or death within 6 months after randomization. Predefined secondary endpoints included pancreatic fistula, total number of interventions, length of hospital and ICU stay, and cost. The primary endpoint occurred in 43% of patients in the endoscopy group and in 45% of patients in the surgery group (risk ratio [RR] 0.97, 95% CI

0.62–1.51; $p=0.88$). Mortality did not differ between groups (nine [18%] patients in the endoscopy group vs six [13%] patients in the surgery group; $p=0.50$), nor did any of the major complications included in the primary endpoint. The rate of pancreatic fistulas and length of hospital stay were lower in the endoscopy group. The authors concluded that an endoscopic step-up approach reduced pancreatic fistula and length of hospital stay, without any evidence for impaired safety. In light of the comparable outcomes and the benefits in secondary endpoints seen with endoscopic treatment, these results make it difficult to endorse surgery as first-line therapy for patients with pancreatic necrosis when endoscopic options exist. The field of interventional endoscopy is rapidly evolving to meet the needs of patients with pancreatitis related complications. A general overview of the management of fluid collections in necrotizing pancreatitis can be seen in Figure 4 below.

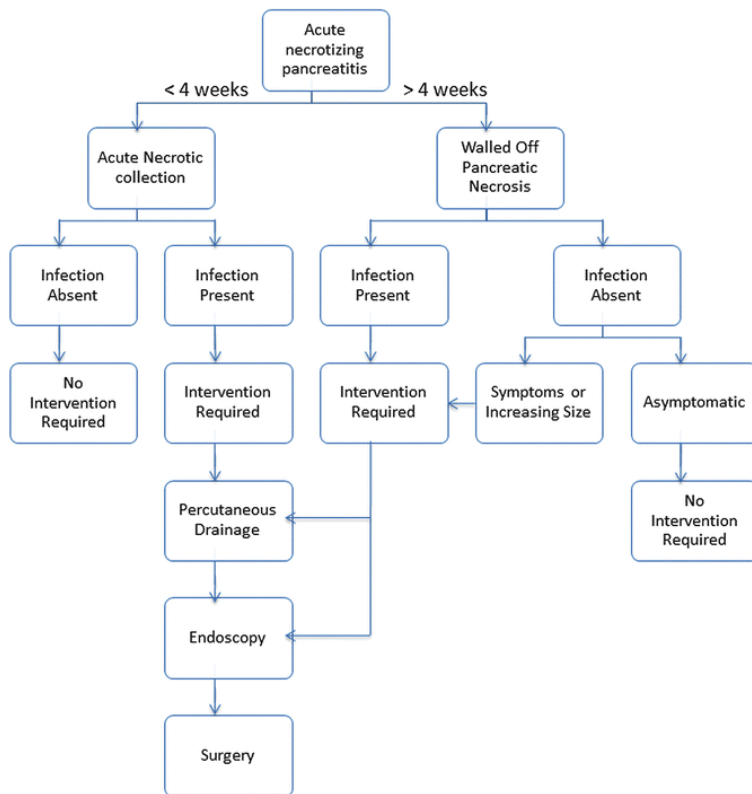


Figure 4. Algorithm for the management of necrotizing pancreatitis.⁶³

Conclusion

AP is one of the most common diseases of the gastrointestinal tract, leading to significant morbidity, mortality and financial burden. Gallstones and alcohol are responsible for nearly 70% of all cases of AP with the remaining 30% attributable to a variety of different etiologies including medications, infectious agents, malignancy and hypertriglyceridemia. Irrespective of the triggering agent, the potential outcomes include a more benign course of interstitial pancreatitis and a more aggressive course of necrotizing pancreatitis. Mortality rates in the setting of infected pancreatic necrosis approach 40%. In order to predict which patients will have a more aggressive course, it is critical to utilize bedside tools such as the BISAP score,

which can aid in guiding management in the early phase. IVF resuscitation should be started early in the clinical presentation and patients should receive either 250cc-500cc/hr of isotonic colloid or IVFs via a goal directed approach with careful attention to hemodynamics, physical examination, and laboratory values such as BUN. The first 12-24 hours after presentation are the most critical, and aggressive IVF resuscitation may have a limited role outside of this window. Despite the historic dogma that patients with pancreatitis should remain NPO to “rest the pancreas”, recent literature advocates for early enteral feeding, with no difference in outcomes between NG and NJ tube feeds. The role of antibiotics in AP is limited to treatment of infected pancreatic necrosis, cholangitis, or other suspected extra-pancreatic infection. There is no role for prophylactic antibiotic therapy to prevent the development of infected pancreatic necrosis. The role of ERCP in AP should be limited to the treatment of cholangitis or ongoing biliary obstruction. There is no role for ERCP in order to mitigate the severity of an episode of AP. Finally, endoscopic interventions for local complications of AP have rapidly evolved over recent years, leading to less invasive management and improved patient outcomes.

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