Acute Pancreatitis – Guidelines to Management
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ABSTRACT

Acute pancreatitis (AP) is a common cause of gastrointestinal emergencies which is associated with significant morbidity and mortality. The diagnosis of AP is established by any two of the following: a) typical symptoms, b) elevated amylase or lipase and c) radiological features. Trans-abdominal ultrasound should be performed in all patients with suspected acute pancreatitis to evaluate the biliary tract and determine the presence of gallstones. The majority of cases of AP are due firstly, to biliary disease and secondly, alcohol use. It is important to determine the severity of AP which will indicate course and prognosis. The prognostic features can be initially assessed by clinical impression, the APACHE II score, the C-reactive protein and evidence of persistent organ failure. The severity of AP is classified as mild, moderately severe and severe. In mild disease, there is no organ failure, local or systemic complications. Patients with moderately severe AP have transient, less than 48 hours, organ failure or systemic complications. Severe AP is associated with persistent organ failure and/or systemic or local complications. The initial management consists of early aggressive fluid resuscitation, 250–500 mL per hour or 5–10 mL per kilogram bodyweight per hour of isotonic crystalloid solution. Use of prophylactic antibiotics is not recommended. Antibiotics should be administered in suspected or confirmed extra-pancreatic infection or infected pancreatic necrosis. Feeding of patients should be commenced early and after adequate fluid resuscitation. The enteral route utilizing a nasogastric tube in patients with gut dysfunction in severe AP and oral feeding in patients with normal gut function in mild AP are appropriate.

Keywords: Acute, management, pancreatitis

INTRODUCTION

Acute pancreatitis (AP) is a common cause of gastrointestinal emergencies and hospital admission (1). It is increasing in incidence and produces significant morbidity and mortality and consumes significant healthcare resources.

The majority of patients with AP will recover fully but one in five will develop severe acute pancreatitis and 20% of these patients may die (2, 3). The management of acute pancreatitis has evolved over the past decade and it is important to develop guidelines on management and update these recommendations at intervals.

Diagnosis

The main presenting feature is abdominal pain. The pain is in the epigastric or left upper abdomen and is usually constant and may radiate to the back, chest, or flanks and may be associated with vomiting. The intensity of the pain is usually severe, but can be variable.

The diagnosis is confirmed by the clinical presentation coupled with an elevation of the serum amylase or lipase above three times the upper limit of normal and characteristic radiological findings. The diagnosis of AP is established by any two of the following three criteria, a) typical symptoms, b) elevated amylase or lipase...
and c) radiological features (4). Serum amylase in AP generally rises a few hours after the onset of symptoms and returns to normal within 3–5 days; however, it may remain within the normal range on admission in up to 20% of patients (4). Compared with lipase, serum amylase returns more quickly to values below the upper limit of normal. Serum amylase concentrations may be normal in alcohol-induced AP and hypertriglyceridaemia (4). Serum lipase has a slightly higher sensitivity for detection of acute pancreatitis, and elevation occurs earlier and last longer than with elevation in serum amylase (2, 3). Serum lipase should be done if the clinical features are in keeping with AP but the amylase is normal. Also, serum lipase should be considered in patients with alcoholism and hypertriglyceridaemia.

Trans-abdominal ultrasound should be performed in all patients with suspected acute pancreatitis. Ultrasonography should be performed at baseline to evaluate the biliary tract and in particular to determine if the patient has gallstones and/or a stone in the common bile duct [CBD] (3). Where point-of-care ultrasound is available, the results should be used to facilitate patient care. Contrast-enhanced computed tomography (CECT) and/or magnetic resonance imaging (MRI) of the pancreas should be reserved for patients in whom the diagnosis is unclear, or failure to improve clinically (4). Computed tomography for the assessment of local complications is most useful 48 to 72 hours after the onset of symptoms rather than at the time of admission (3).

Aetiology

The majority of cases of AP is due to biliary disease (1). The second most common cause is alcohol use. Other causes include: viral, drugs, hypertriglyceridaemia, hypercalcaemia, trauma, endoscopic retrograde cholangiopancreatography (ERCP) and autoimmune. Pancreatic tumour should be excluded in patients over age 40 years. Idiopathic AP is defined as pancreatitis with no aetiology established after initial laboratory (including lipid and calcium levels) and imaging tests (4).

Assessment of severity

It is important to determine the severity of AP which will indicate clinical course and prognosis. The prognostic features can be initially assessed by clinical impression, the Acute Physiology and Chronic Health Evaluation (APACHE 11) score in the first 24 hours, the C-reactive protein (> 15 mg/L), and evidence of persistent organ failure. A serum C-reactive protein (CRP) level of 15 mg/L or greater at baseline or in the first 72 hours is suggestive of severe acute pancreatitis and is predictive of a worse clinical course and should be assessed at admission and daily for the first 72 hours after admission (3). In addition, routine complete blood count along with electrolytes, liver function tests, albumin, triglycerides and an arterial blood gas should be performed.

Two distinct phases of AP have been identified: (a) early, within 1 week, which may be characterized by the systemic inflammatory response syndrome (SIRS) and/or organ failure and (b) late (> 1 week), characterized by local complications. It is critical to recognize the importance of organ failure in determining disease severity and three organ systems should be assessed: respiratory, cardiovascular and renal (5). Local complications include peri-pancreatic fluid collections, pancreatic and peri-pancreatic necrosis (sterile or infected), pseudocysts, and walled-off necrosis (sterile or infected). Isolated extra-pancreatic necrosis is also included under the term necrotizing pancreatitis (4). Local complications should be suspected when there is persistence or recurrence of abdominal pain, secondary increases in serum pancreatic enzyme activity, increasing organ dysfunction, and/or the development of clinical signs of sepsis, such as fever and leucocytosis (5).

The severity of AP is classified as mild, moderately severe and severe. In mild acute pancreatitis, the most common form, there is no organ failure, local or systemic complications and it usually resolves uneventfully in the first week. Patients with moderately severe AP have transient, less than 48 hours, organ failure or systemic complications. Severe AP is associated with persistent organ failure and/or systemic or local complications. Exacerbation of pre-existing co-morbidity, such as coronary artery disease or chronic lung disease, precipitated by the acute pancreatitis is defined as a systemic complication (5).

In patients with severe AP there may be shock (systolic blood pressure < 90 mm Hg), pulmonary insufficiency (PaO2 < 60 mm Hg), renal failure, gastrointestinal bleeding, disseminated intravascular coagulation and metabolic dysfunction. Multi-organ system failure and persistent or progressive organ failure are most closely predictive of mortality and are the most reliable markers of severe disease (2). The prediction of severe disease is best achieved by careful ongoing clinical assessment coupled with the use of a multiple factor scoring system and imaging studies. The APACHE II system is preferred, utilizing a cut off score of eight (2). APACHE II scores should be calculated on admission and daily for the first 72 hours after admission. The APACHE
11 score is based on the following: heart rate, respiratory rate, sodium, potassium, creatinine, haematocrit, white blood cells (WBC), partial pressure of oxygen (PaO2), temperature, mean arterial pressure, pH arterial, Glasgow coma scale. An APACHE II Score of eight or higher at baseline or in the first 72 hours is suggestive of severe acute pancreatitis and is predictive of a worse clinical course (3). It has been shown that obese patients have a significantly increased risk of severe acute pancreatitis (3).

The presence of Systemic Inflammatory Response Syndrome (SIRS) on admission is a predictor of severe pancreatitis and is confirmed by the presence of any two of the following: respiratory rate > 20, heart rate > 90, white cell count < 4 or > 12, temp < 36 °C or > 38 °C (1, 6).

Management

The initial management of AP consists of early aggressive fluid resuscitation (4). Patients with AP usually have intravascular volume depletion due to a number of factors including, vomiting, decreased oral intake and increased third space fluid loss as a result of increased vascular permeability from pancreatic inflammation. This leads to a vicious cycle of pancreatic hypoperfusion and pancreatic necrosis. Early aggressive fluid resuscitation replaces fluid lost and maintains circulatory support which are essential to prevent organ dysfunction. This has been shown to prevent pancreatic necrosis and reduce morbidity and mortality (7, 8).

Early aggressive fluid resuscitation is defined as 250–500 mL per hour or 5–10 mL per kilogram body weight per hour of isotonic crystalloid solution (4). This has been found to be most beneficial in the first 12–24 hours after symptom onset and is of little benefit after 24 hours (9). In a small well designed randomized controlled pilot trial, Lactated Ringer’s (LR) solution was found to be superior to normal saline in reducing systemic inflammatory response syndrome (SIRS) and C-reactive protein (CRP) at 24 hours of hospitalization (10). In a retrospective study evaluating the effect of fluid type used in resuscitation of patients admitted to the Intensive Care Unit (ICU) with AP on hospital mortality and length of ICU stay, mortality was lower in patients who received LR solution compared to isotonic saline. This effect was still observed even after adjusting for confounders (11). Further studies are needed to determine if LR is superior to NS but either LR or NS can be used. Monitoring of fluid resuscitation is crucial and should be performed at frequent intervals especially during the first 48 hours of admission. The adequacy of fluid replacement can be determined by both clinical and laboratory parameters such as urine output (maintain urine output of 0.5–1 mL per kilogram per hour), haematocrit, blood urea nitrogen and creatinine levels.

Caution should be exercised in early aggressive hydration in certain patient populations including the elderly and those with renal and cardiac disease (4, 12, 13). Possible complications of aggressive hydration include fluid overload, pulmonary oedema, abdominal compartment syndrome and death.

Patients with severe pain should be given titrated morphine intravenously or intramuscularly (IM/IV) weight-based starting with 5–10 mg. In patients with mild to moderate pain, a multimodal analgesic regime including nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics and acetaminophen can be considered.

Use of antibiotics

Use of prophylactic antibiotics in AP is not recommended. Antibiotics should be administered in the case of suspected or confirmed extra-pancreatic infection or infected necrosis. The lack of benefit of prophylactic antibiotics has been borne out in several studies. A meta-analysis of 11 randomized controlled trials (RCTs) did not show a significant mortality benefit of prophylactic antibiotics in severe AP (14). A systematic review and meta-analysis of antibiotic prophylaxis in severe AP which included 14 RCTs with a total of 841 patients showed that antibiotic prophylaxis was not associated with a statistically significant reduction in mortality, in the incidence of infected pancreatic necrosis, in the incidence of non-pancreatic infections and in surgical interventions (15). In a multi-centre double-blind placebo controlled trial, early prophylactic antibiotic use in severe AP did not reduce mortality, pancreatic or peri-pancreatic infection and need for surgical intervention (16).

If an infection is suspected, appropriate antibiotics may be started empirically while investigations are done. Once cultures return negative, however, antibiotics should be discontinued.

The mortality rate increases significantly if the course is complicated by infection, with rates as high as 40%. Infections in pancreatitis can be classified into extra-pancreatic infection (pneumonia, urinary tract infection, bacteraemia) and pancreatic infections (infected pancreatic necrosis). Extra-pancreatic infections account for 20% of infected complications in AP.

In patients who develop severe pancreatitis with pancreatic necrosis, the risk of developing pancreatic
infection increases to 40–75% with 24% developing within the first week and 70% after the third week (17). This remains the leading cause of death in patients with severe acute pancreatitis.

Bacterial translocation occurs via three main routes. These include translocation via lymphatics, via haematogenous route or reflux from the duodenum. This results in colonization of the pancreatic necrosis with bacteria and can be seen as early as 8–12 hours after the onset of pancreatitis (17).

It is challenging to diagnose an infection in patients with severe AP as these patients tend to exhibit features of SIRS. Infection should be suspected when: a) on imaging, there is gas configuration in a necrotic collection, b) fine needle aspiration (FNA) of collection yields a positive gram stain or culture, c) very high clinical suspicion (18).

Once it has been established that an infection is present, antibiotics are indicated. These should be broad spectrum such as carbapenems, fluoroquinolones and cephalosporin, which have been shown to have the best penetration into pancreatic tissue and hence, are better at eradication of infections with imipenem having the highest penetration (19). Culture and sensitivity from fine needle aspiration can be used to select targeted antibiotics.

Radiological imaging
The standard first line investigation is an abdominal ultrasound which should be done on presentation or within 24 hours of admission to hospital. All ultrasound images must be digitally acquired and available on the Physics and Astronomy Classification Scheme (PACS) for review. Ultrasound images must be clearly labelled and at a minimum demonstrate the gallbladder (including the neck) in supine and left lateral positions, the intrahepatic biliary tree and the common bile duct.

The indications for CT scan include: a) diagnostic uncertainty, b) patients who present with severe acute pancreatitis (APACHE II > 8), c) failure to respond to initial treatment or clinical deterioration and follow-up and monitoring of established complications, d) guidance of interventional procedures such as percutaneous FNA and/or catheter drainage of fluid collections. The optimal timing for CT is at least 72–96 hours after onset of symptoms. All patients for whom CT is performed should be given a score according the Modified CT Scoring Index scale (Table). All morphological/radiological definitions used should be done according to the Revised Atlanta Classification [Appendix 1] (5).

Magnetic resonance cholangiopancreatogram is indicated in patients with abnormal Liver function tests (LFTs) and common bile duct dilatation that either progressively worsens or fails to settle, where a common bile duct stone is suspected (12).

Table: Modified CT severity index

<table>
<thead>
<tr>
<th>Prognostic indicator</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pancreatic inflammation</strong></td>
<td></td>
</tr>
<tr>
<td>Normal pancreas</td>
<td>0</td>
</tr>
<tr>
<td>Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat</td>
<td>2</td>
</tr>
<tr>
<td>Pancreatic or peri-pancreatic fluid collection or peri-pancreatic fat necrosis</td>
<td>4</td>
</tr>
<tr>
<td><strong>Pancreatic necrosis</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>&lt; 30 %</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 30 %</td>
<td>4</td>
</tr>
<tr>
<td><strong>Extra-pancreatic complications</strong></td>
<td>2</td>
</tr>
<tr>
<td>(pleural effusion, ascites, vascular complications, parenchymal complications, or GI involvement)</td>
<td></td>
</tr>
</tbody>
</table>

Necrotizing pancreatitis
Fine needle aspiration is not indicated routinely because clinical and imaging signs are accurate predictors of infected necrosis in the majority. Image-guided percutaneous drainage should be used first line with surgical necrosectomy reserved for treatment failure.

Indications for intervention (endoscopic/radiological/surgical) include: a) clinical suspicion of, or documented, infected necrosis with clinical deterioration and once walled-off (wait at least four weeks from onset of pancreatitis), b) ongoing organ failure for several weeks in the absence of infected necrosis but walled-off (wait at least four weeks), c) ongoing gastric outlet, intestinal or biliary obstruction due to mass effect (ideally more than four to eight weeks after onset of pancreatitis), d) disrupted pancreatic duct (ideally more than eight weeks after onset of pancreatitis), and e) persistent symptoms in walled-off necrosis without infection [ideally more than eight weeks] (21).

Endoscopic retrograde cholangiopancreatography in acute pancreatitis
There is no benefit in morbidity or mortality for early (24–72 hours) ERCP in the absence of acute cholangitis. The benefit of early ERCP appears to be restricted to those cases in which AP is complicated by acute biliary obstruction and acute cholangitis but not severe AP in the absence of acute cholangitis. Early ERCP in patients
with biliary obstruction without evidence of cholangitis confers no benefit (22).

A meta-analysis found no difference in incidence of local pancreatic complications or mortality when early ERCP was employed to manage both predicted mild and severe AP compared to conservative treatment. A second meta-analysis was designed to negate the confounding effect of acute cholangitis. This study demonstrated that in patients with predicted mild or severe AP without cholangitis, there was no benefit for early ERCP over conservative treatment [complications or mortality] (23, 24).

Cumulatively, the evidence for the role of therapeutic ERCP in AP suggests that early ERCP is indicated in patients with AP if there is clinical evidence of acute cholangitis, but not for those with cholestasis alone (25). Fortunately, the majority of gallstones that result in AP will readily pass into the duodenum (26). Cholestasis alone may reflect ampullary oedema secondary to stone passage and should improve over the first few days of admission. Persistent cholestasis without cholangitis may require ERCP but not usually in the acute setting.

**Nutrition**
Clinical and experimental studies have shown that bowel rest in AP is associated with detrimental intestinal mucosal atrophy and bacterial translocation from the gut (27). In comparison, several studies have demonstrated that the use of early nasogastric tube feeding in AP patients (within 24 hours of admission) resulted in shorter hospital stay, decreased infectious complications, decreased morbidity and decreased mortality (27–30).

For patients with mild AP, the timing of re-feeding remains somewhat controversial. Studies have determined that immediate oral feeding in mild AP appears to be safe (31). A randomized study revealed that starting...
enteral nutrition within 24 hours of hospital admission resulted in a significant decrease in intensity and duration of abdominal pain (32). Early nutrition is, however, not without an element of risk, particularly in haemodynamically unstable patients and in those requiring ionotropic support (33). In order to avoid potentially life-threatening non-occlusive mesenteric ischaemia, patients with severe AP should commence enteral nutrition after adequate fluid resuscitation and stabilization (34).

In addition to the timing of feeding, the type of enteral feed has been examined in some detail. A low-fat solid diet introduced early in the course of mild AP appears to be as safe as clear fluids (35). The low-fat solid diet actually provides more calories and shortens hospital stay (36, 37). A recent meta-analysis revealed that expensive semi-elemental and elemental formulae conferred no advantage over standard polymeric formulae (38).

Several randomized trials and two meta-analyses comparing parenteral nutrition (PN) and enteral nutrition (EN) in the management of predicted severe pancreatitis showed a two-fold reduction in risk of total and pancreatic infectious complications and a 2.5-fold reduction in risk of death in patients receiving EN (23, 28, 30, 31, 39, 40).

As a guideline, on presentation, patients suspected with a diagnosis of AP should have a nasogastric tube passed and instructed on no oral intake on the first day, and feeding of patients with AP should be commenced on the second day of hospital admission and after adequate fluid resuscitation. The EN route utilizing a nasogastric tube in patients with gut dysfunction in severe AP and oral feeding in patients with normal gut function in mild AP are appropriate (41).

**Surgery in acute gallstone pancreatitis**

Patients with gallstone pancreatitis may require surgery to treat complications of the pancreatitis. In patients with severe pancreatitis and infected necrotic tissue, surgery is the best option for management of this complication (42). The principles remain with the 3Ds: delay, drain, debridement while in the ICU. The timing of surgery is delayed up to after four weeks until any collection has walled-off and separated from viable tissue allowing for a minimally invasive approach (endoscopic or video-assisted retroperitoneal necrosectomy) rather than the traditional open surgery (42, 43). While a multidisciplinary approach must be adopted, open surgery is now reserved for situations where minimally invasive approach is not available and for cases refractory to minimally invasive interventional approaches.

Surgery is also recommended to prevent recurrence of the pancreatitis. Cholecystectomy is the definitive treatment for gallstones and laparoscopic cholecystectomy is the preferred route. The timing of laparoscopic cholecystectomy after an attack of acute biliary pancreatitis is controversial. However, overwhelming evidence indicate that in patients with mild AP due to gallstones, early laparoscopic cholecystectomy during the index admission is safer and associated with less postoperative complications and shorter overall duration compared to delayed laparoscopic cholecystectomy and is an overall indicator of quality of care (44–46).

Open cholecystectomy is the acceptable alternative if laparoscopic cholecystectomy is not available. Cholecystectomy should be delayed in patients with severe pancreatitis, with or without peri-pancreatic collections until the collections either resolve or if they persist beyond six weeks, at which time cholecystectomy can be performed safely (12, 47).

The likelihood of finding stones in the CBD was found to be 70% at admission, decreasing to 20% after four days (47). The general recommendation for patients undergoing surgery for mild acute biliary pancreatitis is for evaluation of the CBD for stones using intra-operative cholangiogram, however other options include endoscopic ultrasound and magnetic resonance imaging (48, 49). Routine intra-operative cholangiogram at the time of cholecystectomy may be unnecessary, especially if preoperative biochemical and imaging markers do not indicate an increased likelihood of CBD stones (48). Magnetic resonance cholangiopancreatography correlates well in patients with normal CBD and reduces the need for ERCP or intra-operative cholangiogram (49). It does have false positive and false negative rates of about 10% which should be considered in the management of the patient (50).

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APPENDIX 1

REVISED DEFINITION OF MORPHOLOGICAL FEATURES OF AP (Atlanta Classification)

1. **Interstitial oedematous pancreatitis**
   - Acute inflammation of the pancreatic parenchyma and peri-pancreatic tissues, without recognizable tissue necrosis
   - Contrast enhanced computerized axial tomography (CECT) criteria
   - Pancreatic parenchymal enhancement by intravenous contrast agent
   - No findings of peri-pancreatic necrosis

2. **Necrotizing pancreatitis**
   - Inflammation associated with pancreatic parenchymal necrosis and/or peri-pancreatic necrosis
   - CECT criteria
   - Lack of pancreatic parenchymal enhancement by intravenous contrast agent and/or
   - Presence of findings of peri-pancreatic necrosis

3. **APFC (acute peri-pancreatic fluid collection)**
   - Peri-pancreatic fluid associated with interstitial oedematous pancreatitis with no peri-pancreatic necrosis. Applies only to areas of peri-pancreatic fluid seen within the first four weeks after onset of interstitial oedematous pancreatitis and without the features of a pseudocyst.
   - CECT criteria
   - Occurs in the setting of interstitial oedematous pancreatitis
   - Homogeneous collection with fluid density
   - Confined by normal peri-pancreatic fascial planes
   - No definable wall encapsulating the collection
   - Adjacent to pancreas (no intra-pancreatic extension)

4. **Pancreatic pseudocyst**
   - Encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis. Usually occurs more than four weeks after onset of interstitial oedematous pancreatitis.
   - CECT criteria
   - Well circumscribed, usually round or oval
   - Homogeneous fluid density
   - No non-liquid component
   - Well defined wall; that is, completely encapsulated
   - Maturation usually requires > 4 weeks after onset of acute pancreatitis; occurs after interstitial oedematous pancreatitis

5. **ANC (acute necrotic collection)**
   - A collection containing both fluid and necrosis associated with necrotising pancreatitis; necrosis involve the pancreatic parenchyma and/or the peri-pancreatic tissues
   - CECT criteria
   - Occurs only in the setting of acute necrotizing pancreatitis
   - Heterogeneous and non-liquid density of varying degrees in different locations
   - No definable wall encapsulating the collection — intra-pancreatic and/or extra-pancreatic

6. **WON (walled-off necrosis)**
   - A mature, encapsulated collection of pancreatic and/or peri-pancreatic necrosis that has developed a well defined inflammatory wall. WON usually occurs > 4 weeks after onset of necrotizing pancreatitis.
   - CECT criteria
   - Heterogeneous with liquid and non-liquid density with varying degrees of loculations (some may appear homogeneous)
   - Well defined wall, that is, completely encapsulated
   - Location — intra-pancreatic and/or extra-pancreatic
   - Maturation usually requires four weeks after onset of acute necrotizing pancreatitis

**Infected Necrosis**
   - The diagnosis of infection (infected necrosis) of an ANC or WON can be suspected by the clinical course or the presence of gas within the collection seen on CECT. This extraluminal gas is present in areas of necrosis and may form a gas/fluid level. In cases of doubt, fine needle aspiration for culture may be performed.