

What guidelines tell us about acute pancreatitis. A review of the last international guidelines

Review Article

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Abstract: Background. Since the Atlanta Symposium several guidelines and consensus conferences have been published to improve the management and understanding of patients with acute pancreatitis. Herein, a review of the most recent guidelines on acute pancreatitis is carried out, trying to find differences and similarities. Methods. Five of the last international guidelines on acute pancreatitis as well as the last consensus conference are critically reviewed. Conclusions. There is more consensus than disagreement between guidelines, which is why the knowledge of them is of great importance when treating AP.

Keywords: *Pancreatitis • Review • Necrotizing pancreatitis • Guidelines*

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1. Introduction

Acute Pancreatitis (AP) is a prevalent disease with a wide severity range. Its management involves many different medical and surgical specialists with different strategies according to clinical severity.

During the last 10 years, several practice guidelines have been published, in order to specify management recommendations on acute pancreatitis patients.

Since the 2002 International Association of Pancreatology (IAP) Guidelines for the Surgical Management of Acute Pancreatitis [1], several Medical or Surgical Associations have developed Practice Guidelines. We reviewed the IAP Guideline above mentioned, together with the UK Guidelines for the management of acute pancreatitis [2]; the Practice Guidelines in Acute Pancreatitis directed by the American College of Gastroenterology [3]; the Treatment strategy for acute

pancreatitis Guidelines from the Japanese Society of Hepato-Biliary-Pancreatic Surgery [4]; and the Spanish Biliopancreatic Club recommendations on acute pancreatitis treatment [5].

We consider all guidelines are the reflection of hard work and consensus, and all of them have something to contribute. That is why we considered reviewing all of the above mentioned guidelines remarking their agreements and differences in an attempt to finally summarise "What Guidelines tell us about Acute Pancreatitis".

2. Definitions

Acute Pancreatitis is defined as the acute nonbacterial inflammatory condition of the pancreas, derived from early activation of digestive enzymes found inside the

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acinar cells, with variable compromise of the gland itself, nearby tissues and other organs [6].

In order to clarify all concepts among medical communities, an International Symposium was held in Atlanta in 1992, where the most important features were cleared. Some of the newer guidelines still apply the definitions of the Atlanta symposium, but their unspecificity and certain aspects of the definitions have been criticized by others. In addition, concepts such as severity or organ failure have been more carefully defined in the newer guidelines.

Recently a multidisciplinary consensus proposed modified definitions for AP and its complications [7]. According to this new consensus acute pancreatitis (AP) is defined as either interstitial or necrotizing. The former is usually clinically mild and the latter clinically severe. Necrotizing pancreatitis is defined by the lack of enhancement of pancreatic parenchyma on cross-sectional imaging after intravenous contrast administration and can involve pancreatic parenchyma alone, pancreatic parenchyma and peripancreatic tissues, or peripancreatic tissues alone. Some of the proposed terms in this review are as follows:

1. Acute peripancreatic fluid collections, which arise in the setting of interstitial pancreatitis, are adjacent to the pancreas, homogeneous, fluid filled, and without full encapsulation. They occur fewer than 4 weeks after the onset of AP.
2. Acute necrotic collections, which occur in necrotizing pancreatitis, can be intrapancreatic or extrapancreatic, heterogeneous, contain non liquid material with varying amounts of fluid, and are without full encapsulation. They occur less than 4 weeks after the onset of AP.
3. Pseudocysts comprise only a minority of collections in pancreatitis, develop adjacent to the pancreas, are homogeneous, fluid filled, with a defined wall, lack significant non liquid debris, and occur at least 4 or more weeks after the onset of AP.
4. Walled-off necrosis (WON), which occurs only in the context of acute necrotizing pancreatitis, can be intrapancreatic or extrapancreatic. is heterogeneous.

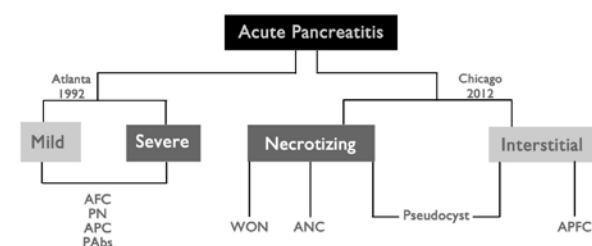


Figure 1. Differences between definitions on Atlanta 1992 and Chicago 2012. AFC: acute fluid collection; PN: pancreatic necrosis; APC: acute pseudocyst; PABs: pancreatic abscess; WON: walled-off necrosis; ANC: Acute necrotic collection; APFC: acute peripancreatic fluid collection

contains non liquid material with varying amounts of fluid, and has an encapsulating wall. This process occurs 4 or more weeks after the onset of AP.

Figure 1 includes the definitions of the Atlanta Symposium as well as those from the last Chicago consensus [7]. Additionally a graphical explanation of the new proposed terms is shown on Figure 2.

3. Diagnosis

Diagnosis of Acute Pancreatitis is based on clinical [1], biochemical [2] and radiological [3] criteria as mentioned in American and Japanese guidelines. The British guidelines consider only the first two criteria sufficient to establish a diagnosis.

AP is clinically presented as an acute abdominal pain and tenderness in the upper abdomen, usually epigastric and radiated to the back, associated with fever, nausea, vomiting and anorexia.

Biochemical elevation of pancreatic enzymes (amylase and lipase) in blood. The American guidelines diagnose AP when elevation is 3 times higher than normal, while the British guidelines remark that “values should be interpreted in the light of the time since the onset of abdominal pain” [2]. They all agree that although amylase is widely available and provides acceptable accuracy of diagnosis, lipase is preferred for the diagnosis of AP when possible.

Radiological abnormalities in the pancreas is the last criteria for AP diagnosis. The American and British guidelines consider CT scan as the best imaging technique to use when diagnosis is unclear; the Japanese guidelines consider ultrasonography as one of the diagnostic procedures to be performed first. MRI is also considered of great accuracy in the Japanese guideline. Probably the first step to investigate the differential diagnosis in acute abdomen is ultrasonography. Furthermore, it can also determine the presence of bile stones, hence giving clues as to AP etiology.

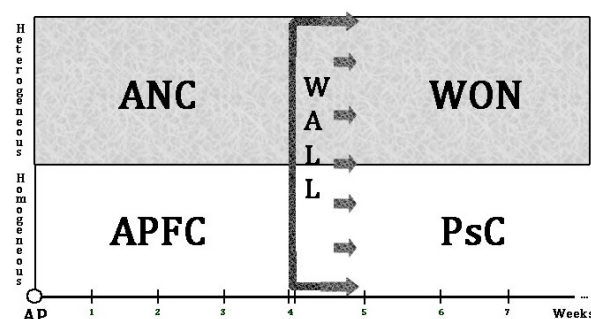


Figure 2. Revised terms in new consensus; ANC: acute necrotic collection; APFC: acute peripancreatic fluid collection; WON: walled-off necrosis; PsC: pseudocyst

4. Assessment and prediction of severity

Initially the most common cause of mortality was associated with early severe inflammatory response, which nowadays has decreased due to intensive care unit management. Now mortality is associated with late septic complications, which is why severity should be assessed and predicted.

When AP diagnosis is confirmed, patients should be classified as mild or severe in order to receive appropriate treatment and management either in the ward or in an intense care unit (ICU) respectively.

American, British and Spanish guidelines maintain the Atlanta 1992 criteria for mild and severe AP, while Japanese use a severity scoring system (JPN score) dividing AP into mild, moderate, severe (I, II) and extremely severe.

Once severity is determined, patients should be admitted either in the ward or in ICU and reassessed every 24 hours or less, particularly during the first three days.

Multiple severity scores have been proposed in order to predict severity and diminish mortality, but guidelines disagree on which one is the best. Occidental guidelines recommend APACHE II/APACHE II-O as the best predictor score available, while Japanese guidelines prefer the Japan Score. Regardless of the severity predictor used, what should remain clear is the need of periodical determination of predicted severity of every patient diagnosed with AP, as well as the identification of multiorgan failure and/or local pancreatic complications.

Guidelines advocate the usefulness of two lab tests in predicting severity. The first one is hematocrit, which, when periodically obtained, can gauge adequacy of fluid resuscitation during the first day and possibly reflects necrotizing pancreatitis if elevated (≥ 44). The second one is the C-reactive protein (CRP). Plasma levels greater than 150 mg/L after 48 h of admission also correlate with the presence of necrosis.

5. Imaging in AP

5.1. Computed Tomography (CT Scan)

There are several occasions when CT Scan can be indicated during the evolution of AP. All of them are recommended, but not mandatory. The first recommendation for performing a CT Scan is during admission. It can help to distinguish between AP and other entities causing intense abdominal pain. The second is when differentiating between interstitial and necrotizing pancreatitis

due to prognosis implications. Guidelines also recommend a CT Scan to be performed for detecting local complications in patients with persistent organ failure, signs of sepsis or deterioration in clinical status 6-10 days after admission. Finally, a control CT Scan should also be performed whenever clinical status deteriorates or fails to improve, and even when improving, to detect asymptomatic complications such as pseudocysts or arterial pseudoaneurism.

CT scan provides important information in accordance with Balthazar criteria for severity. When IV contrast is used, a CT severity index can be obtained. This index assigns points on the basis of the CT grade (A-E) and the amount of necrosis (none, less than 30%, 30-50%, greater than 50%). Patients with necrotizing pancreatitis have higher morbidity and mortality rates than patients with interstitial disease.

5.2. Magnetic Resonance Imaging (MRI)

MRI is considered as useful as CT for severity assessment with the advantage of less nephrotoxicity, no x-ray exposure and for obtaining additional information on the pancreatic duct and biliary system. It also has some disadvantages such as lack of emergency accessibility, the removal of infusion pumps during performance and the time spent on the procedure.

6. Medical management

6.1. Initial Management/Supportive Care

Guidelines remark three initial therapies as crucial: fluid resuscitation, hypoxemia prevention and pain relief.

Fluid Resuscitation: intravenous fluid replacement should start early so as to counteract hypovolemia produced by third space losses, vomiting, diaphoresis and increased vascular permeability. Adequacy of fluid resuscitation should include the measuring of clinical parameters such as vital signs and urinary output (>0.5 ml/kg body weight), as well as laboratory parameters, especially hematocrit [8].

Hypoxemia Prevention: the administration of supplemental oxygen is recommended during the first 24-48h and arterial oxygen saturation must be maintained higher than 95%. When SO_2 is $\leq 95\%$ or laboured respiration is detected, arterial blood gas analysis should be extracted and hypoxemia corrected.

Pain Relief: this is also one of the priorities in supportive care of AP. Analgesic drugs should be chosen stepwise, from non-opioids to narcotics, depending on clinical presentation. Japanese guidelines recommend

buprenorphine as the best non-narcotic analgesic, while Spanish guidelines recommend locoregional analgesia if opioids are not sufficient. Spanish guidelines are unique in their recommendations to prevent recurrent pain after oral intake reintroduction, with intramuscular injection of lantreotide [5].

All supportive care treatments contribute to minimize pancreatic necrosis and also prevent intestinal ischemia resulting in bacterial translocation and secondary pancreatic infection.

6.2. Specific Drug Therapy

Guidelines differ on specific AP treatment. On one hand the Japanese guidelines recommend and systematically use continuous IV infusion of a large dose of protease inhibitor to reduce frequency of complications and mortality rate. On the other hand, the British guidelines claim there is no proven therapy for AP.

6.3. Nutritional Support

Nutrition in patients with AP is of great importance due to its hypermetabolic nature, which induces caloric-protein malnutrition. Nutrition should be adequate to clinical status. In patients with mild pancreatitis, oral intake should be initiated when pain has subsided, in the absence of nausea or vomiting, and if signs of peristalsis are present. This scenario usually occurs within the first 3-7 days of hospitalization.

In severe AP artificial nutrition should be initiated, in order to prevent complications and provide long-term nutritional support, when it becomes clear that the patient would not tolerate oral food intake for several weeks. The American guidelines recommend this decision should be made within the first 3-4 days of illness, while the Japanese guidelines propose early introduction of artificial nutrition. Spanish guidelines recommend starting with artificial nutrition within the first 72 hours.

All guidelines agree that the preferred route of nutrition is enteral. This route has potential benefits as opposed to parenteral, regarding the reduction of infection and surgery rates, as well as shorter hospital stay [9]. These benefits respond to the theoretical benefit of preserving the mucosal function and limiting inflammatory response. However several randomized controlled trials (RCT) have shown no differences neither in mortality nor in morbidity other than infection [4]. The majority of studies have reported enteral feeding via a nasojejunal tube; nevertheless some of them now compare nasogastric and nasojejunal tube nutrition, finding them similar in safety, morbidity and mortality [10], as well as

considering nasogastric tube nutrition feasible in about 80% of all cases [11].

When patients do not tolerate sufficient enteral feeding, combined enteral and parenteral nutrition is recommended. In the case of local and systemic severe complications or impossibility of enteral nutrition, total parenteral nutrition should be used instead.

6.4. Prophylactic Antibiotherapy

In the case of mild AP there is no need to use antibiotic prophylaxis.

In severe AP, guidelines do not make a clear recommendation about antibiotic prophylaxis. Some recommend prophylaxis with broad spectrum and good pancreatic tissue penetration antibiotics. This recommendation is based on several RCT showing decreased infectious complications and mortality rate [12-14]. British guidelines go further, proposing that antibiotic prophylaxis should be considered only for patients with CT evidence of more than 30% necrosis of the pancreas although no evidence exists to support this view. If prophylaxis is initiated Spanish guidelines recommend maintaining up to 14 days, unless local or systemic non-septic complications persist or C-reactive protein remains higher than 120 mg/dl.

Nonetheless, recent RCT show no benefit of prophylactic antibiotherapy in severe AP. One recently published updated meta-analysis found no support on antibiotic prophylaxis [15].

7. Complications and their management

During the first two weeks after the onset of acute pancreatitis patients may develop both systemic inflammatory response syndrome (SIRS) and parenchyma necrosis. After the second week a new stage in AP begins with development of infectious pancreatic complications such as infected pancreatic necrosis or pancreatic abscess. Infectious complications increase mortality rates and should be managed promptly and accurately. The following items are the most important complications and their management.

7.1. Sterile Pancreatic Necrosis

Most patients with sterile pancreatic necrosis recover in response to conservative nonsurgical management. All guidelines agree on medical treatment as a first approach. This recommendation is based on multiple retrospective studies and prospective randomized trials,

which found increased mortality in patients undergoing early debridement. In fact, most patients will not require surgery. In any case it is recommended to wait as long as possible (around 3–4 weeks [16]) before performing necrosectomy in order to allow borders between normal and necrotic pancreatic tissue to become distinct, thus minimizing haemorrhage and avoiding unnecessary pancreatic tissue resection. Nevertheless, some reports state that failure of recovery after 1 or 2 weeks of intensive medical treatment should be an indication for surgery, irrespective of infection [17].

7.2. Infected Pancreatic Necrosis

Approximately 33% of patients with necrotizing pancreatitis develop infected necrosis [18]. Differentiation between sterile and infected pancreatic necrosis (IPN) is essential, because of the differences in management, prognosis and mortality rate.

IPN must be suspected and confirmed if patients develop signs of sepsis or organ failure after initial improvement. A contrast-enhanced CT scan should be performed to detect the presence of gas bubbles in the necrotic area. Image-guided fine needle aspiration (FNA) of the suspected area followed by Gram stain and culture of tissues/fluids confirm diagnosis. However, recent consensus [7] agrees on avoiding diagnostic interventions such as FNA, recommending minimally invasive percutaneous or endoscopic interventions early in the course of the disease either to avoid or postpone more invasive surgical interventions. Moreover, there is potential for the treatment of infected necrosis with antibiotics alone when there are no signs of sepsis.

Minimally invasive interventions consist in endoscopic and image-guided percutaneous drainage, while surgical interventions are classified into open and laparoscopic or retroperitoneoscopic approaches.

Guidelines mention that either radiological or surgical interventions are possible; however, standard surgical practice maintains that all patients with infected necrosis should undergo necrosectomy. Nowadays a new vision of IPN management is proposed and supported by RCT. This new management strategy is called step-up approach. It consists in several consecutive

steps starting with minimally invasive techniques to control infected necrosis, with definitive necrosectomy deferred or sometimes avoided altogether, based on the clinical course of the patient. The first step is the placement of a percutaneous catheter drainage (PCD), preferably into the retroperitoneum, with the percutaneous transabdominal or endoscopic transluminal routes as options. If no clinical improvement is seen after 72h, a new percutaneous drainage should be placed followed by video assisted retroperitoneal debridement. If this fails, open surgical necrosectomy should be performed. There is consensus, but limited data to support the claim that postoperative continuous irrigation and “closed packing” are superior to open packing and planned relaparotomies [7].

7.3. Gallstone Pancreatitis

All guidelines agree in the early use of ERCP in patients with severe or predicted severe acute pancreatitis associated with colangitis, jaundice, post cholecystectomy or dilated common bile duct. The procedure is best carried out within the first 72 hours after the onset of pain. When an ERCP is handled, a sphincterotomy or duct stenting should be used to ensure relief of obstruction. If ERCP is not available, then biliary surgical exploration should be performed.

Cholecystectomy in mild gallstone AP should be done either during the same hospital admission, or within the next two weeks.

In summary, in this review we have examined the recent world guidelines for AP. We have tried to identify similarities and differences regarding definitions, diagnosis, prediction, assessment, and management of the disease. As we have seen, although the guidelines refer to the same disease, they present some differences. However there is more consensus than disagreement, which is why the knowledge of these guidelines is of great importance when treating AP.

Conflict of interest statement

Authors state no conflict of interest.

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