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Management of acute pancreatitis in emergency

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Abstract. – This review focuses on the medical and endoscopic approachs to patients with acute mild or severe pancreatitis. Acute pancreatitis is an acute inflammatory process of the pancreas whose the main determinant of the outcome is the extent of pancreatic necrosis. After the diagnosis, a severity assessment using scoring systems and early contrast enhanced Computed Tomography should be performed in all patients within 48 hours from the admission.

All cases of severe acute pancreatitis should be managed initially in intensive care units with full systems support. Patients with gallstone pancreatitis should have definitive Endoscopic Retrograde Colangio-Pancreatography (ERCP) or surgical management of the gallstones.

Key Words:

Acute pancreatitis, Management, Medical support, Endoscopic treatment.

Introduction

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas, with variable involvement of other regional tissues or remote organ systems[1]. According to the Atlanta classification[2], there are two forms of AP: mild and severe. Mild AP is characterized by interstitial oedema of the gland, while severe causes the necrosis of parts of the pancreas and is associated with organ failure and/or local complications such as pseudocysts or abscess. The distinction between these two forms is difficult and appears somewhat arbitrary, since often patients are admitted to the hospital with what appears to be mild disease that, later on, deteriorates to severe pancreatitis[3].

In severe AP, the involved tissue releases cytotoxic substances that cause a severe dysfunction of multiple organ systems: the patients typically show an increased alveolar to arterial oxygen gradient, a reduced ejection fraction, a reduced creatinine clearance, an increase in serum bilirubin, a decrease in platelets and clotting factors, agitation or coma. As the disease progresses, multi-organ dysfunction becomes multi-organ failure[4]. This condition requires some external interventions to maintain homeostasis such as mechanical ventilation, inotropes and vasopressors, renal replacement therapy, continuing blood transfusions[3-5]. The mortality is about 25%-50%[6] and outcomes depend on a variety of factors, including the extent of necrosis and the onset of other complications such as infections[7,8].

The commonest causes of pancreatitis are the alcohol abuse or the bile duct obstruction[9]. Other causes include drugs, trauma, Endoscopic Retrograde Colangio-Pancreatography (ERCP), metabolic diseases: i.e. hypertrygliceridemia, infections, hypothermia[10].

As regards the differential diagnosis it is important to exclude other life threatening conditions: the mesenteric ischaemia, the visceral perforation or the leaking abdominal aortic aneurysm[11].

The management of AP can be divided into three phases: (1) the diagnosis and assessment of severity; (2) the management according to the disease severity; (3) the detection and management of the complications and the evaluation and treatment of aetiological factors.

Diagnosis

AP may be diagnosed by the history (abdominal pain, nausea and vomiting, shock, tender abdomen, respiratory distress), by the elevation of serum amylase and lipase in excess of three times the upper limit of normal[12], and by contrast-enhanced computed tomography (CT).

Clinical Approach

The abdominal pain varying from mild to severe is the major symptom of AP. It is constant and dull; usually it worsens when the patient is supine[9]. Nausea, vomiting or diffuse abdominal tenderness are common clinical findings due to gastric and intestinal hypomobility[13]. These features occur in several other acute abdominal diseases, and a diagnosis of AP is often unreliable if established on the clinical findings alone. Physical examination reveals tachycardia and low fever. Occasionally, body wall ecchymoses (Cullen's sign at the umbilicus, Grey-Turner's sign in the flanks) indicate a severe necrotizing pancreatitis[14].

Biochemical Approach

In uncomplicated pancreatitis, the serum amylase level increases from 2 to 12 hours after the onset of symptoms reaching a peak after 12 to 72 hours and usually returns to normal within one week[15]. The sensitivity of the test is around 85% and it's specificity 40%. Amylase testing is quickly performed, easily obtained and inexpensive[16]. However, a small increase of amylase can occur in a variety of other conditions such as mesenteric ischemia, perforated peptic ulcer, intestinal obstruction, biliary colic, renal failure, tubo-ovarian disease and macroamylasemia[17]. Lipase levels increase six hours after the onset of clinical symptoms reaching a peak at about 24 hours and a decrease within 8 to 14 days. The specificity and sensitivity are respectively 85% and 95%, particularly in detecting alcoholic pancreatitis[18]. The degree of amylase and lipase elevation does not reflect the severity of the pancreatic damage. The most accurate serum indicator for AP is trypsin elevation[19]. However, a serum trypsin essay is not widely available and therefore is not routinely used.

Recently a rapid urinary trypsinogen-2 test strip as screening test for AP has been developed. If positive, this test identifies patients who need further diagnostic tests, and can be performed in health care units where laboratory testing facilities are not immediately available[20].

The determination of serum C-reactive protein (CRP) is widely used for the assessment of the severity of AP[21]. Serum levels of this protein greater than 100 mg/L indicate a severe AP in about 60%-80% of the cases. The determination of the CRP is easy to perform and inexpensive[22,23]. The sensitivity of this test is 73%, and the specificity is 71%.

Initial hematocrit appears to be an early, simple, and useful predictor of severe pancreatitis. In particular, some studies suggest that a 5% increase of the hematocrit is a significant predictor of severe pancreatitis, length of stay and of pancreatic necrosis[24,25]. Leukocytosis frequently occurs.

Other laboratory features include hyperglycemia, hypocalcemia, hyperbilirubinemia and mild elevations in serum alanine aminotransferase (ALT) and alkaline phosphatase. A serum bilirubin greater than two and half times normal levels and a serum ALT more than twice the normal levels are suggestive of gallstone pancreatitis[26].

Another important test to perform in the emergency room is the arterial blood gases. The presence of a hypoxemia (arterial pO_2< 60 mmHg) may herald the onset of adult distress syndrome[27].

Finally the electrocardiogram may show abnormalities such as ST and T waves alterations due to the myocardial ischemia.

Instrumental Approach

Most authorities recommend that radiographs of the chest and abdomen should be obtained on presentation to exclude a bowel perforation or an early pulmonary complication[9].

Ultrasonography is indicated when the clinical presentation or the laboratory assessments suggest a biliary disease. A swollen pancreas may be detected, but the gland is poorly visualised in 25-50% of cases, so this method cannot be used for a definitive diagnosis[28].

A dynamic contrast-enhanced CT scan is recommended for patients in which severe pancreatitis is suspected[29]. Balthazar et al[30,31] have demonstrated that contrast enhanced

CT is able to assess the severity of AP and that there is a close correlation between the presence of necrosis and the course of hospitalization including morbidity and mortality. On these basis they classified the severity of AP into 5 categories and they found that the mortality was nil in stages A, B and C, and reached 17% in those of grade E (Table I).

If available, magnetic resonance is a reliable method of staging acute pancreatitis severity and has predictive value for the prognosis. It also has fewer contraindications than CT, and is able to detect a pancreatic duct disruption, which may occur early in the course of AP[32].

Severity Assessment

A prompt identification of patients who need intensive care or subspeciality consultation is crucial. Many scoring systems are used to detect the presence of severe pancreatitis, to predict the deterioration of a mild form, to compare the severity of the disease within and between patients and to select the patients for specific treatment strategies as soon as possible[33,34].

The Ranson score is still the most popular method for judging the severity of pancreatitis. Ranson et al[35] identified in 1974 a series of 11 criteria. Five of them are calculated upon hospital admission and 6 in the following 48 hours. Patients with less than two positive items survived; in those with 3 or 5 positive items, the mortality rate was about 20%, and in those with 6 or more positive items, the mortality reached about 50% (Table II). However, the Ranson score is criticized because it requires 48 hours of observation for the judgement of severity, thus delaying the proper treatment after the onset of pain. Furthermore, the threshold for abnormal values largely depends on whether the pancreatitis is caused by alcohol or gallstones. The sensitivity of the score is only 73%, and the specificity is 77%.

Table I. Balthazar score.

Grade A:	Normal
Grade B:	Focal or diffuse enlargement of the pancreas
Grade C:	Pancreatic gland abnormalities associated with peripancreatic inflammation
Grade D:	Fluid collection in a single location
Grade E:	Two or more fluid collections and/or the presence of gas in or adjacent to the pancreas

Table II. Ranson's criteria.

On admission:	Age > 55 years
	WBC > 16000 mm^3
	Glucose > 11 mmol/l
	LDH > 400 IU/l
	AST > 250 IU/l
Within 48 hours:	Decrease in Hct > 10%
	Increase in Urea > 1.8 mmol/l
	Calcium < 2 mmol/l
	PaO_2 < 8 kPa
	Base deficit > 4 mmol/l
	Fluid deficit > 6 l
Risk factors/Mortality:	0-2 < 1%
	3-4 ~ 15%
	5-6 ~ 40%
	> 6 ~ 100%

The Acute Physiology and Chronic Health Evaluation (APACHE II score)[37] which takes into consideration age, presence of chronic associated diseases and some biochemical parameters has been proposed for the assessment of the severity of acute pancreatitis.

The assessment is performed at the time of admission and may be repeated daily to monitor the disease progression. However, it is very cumbersome for routine clinical use. The sensitivity is 77%, and the specificity is 84%.

Etiologic Diagnosis

It is essential to establish the etiology of pancreatitis since in many cases treatment of specific causes of pancreatitis (e.g. gallstones) resolve the progression of the disease.

First Line Medical Treatment

The choice of treatment is based on the severity of the attack. If no complications are present, the care usually focuses on relieving the symptoms and supporting the body functions[38].

The treatment of severe AP is complex and requires a day-by-day and week-by-week re-evaluation of the patients' conditions with the treatment tailored to the changes that rapidly

occur in the critically ill patients. Goals of the treatment include: supportive care, reduction of pancreatic exocrine secretion ("resting of the pancreas") and, thereby, prevention of pancreatic necrosis or abscess formation and limitation of systemic complications[39].

Mild Pancreatitis

Management of mild pancreatitis is supportive: cornerstones of the treatment are fluid replacement by intravenous dextran, promoting hemodilution[40], and infusion of analgesics to relief the pain. Meperidine along with an antiemetic is preferred over the use of morphine, because morphine may cause spasm of the sphincter of Oddi, which has the potential to worsen the condition[41].

Since the main physiopathologic mechanism of pancreatitis is the autodigestion of the pancreas and peripancreatic tissues by activated enzymes, patients with moderate pancreatitis must initially avoid food and liquids because eating and drinking stimulate the pancreas to produce more enzymes ("resting of the pancreas")[42].

In patients with mild uncomplicated pancreatitis, no benefit is observed from nutritional support and the energy intake received with intravenous dextrose 5% in water generally suffices[43].

Refeeding is instituted once the pain subsides and the patient is hungry. Usually, normal eating can resume after 2 to 3 days without further treatment. Once oral intake is tolerated, patients can be discharged from the hospital. The diet should be low in fat and proteins.

A nasogastric tube is needed only for vomiting or severe pain or if a paralytic ileus develops[44].

Antibiotics should not be administered routinely as there is no evidence that their use in mild cases will affect the outcome or reduce the incidence of septic complications[45].

Severe Pancreatitis

Severe pancreatitis is often associated with a marked increase in microvascular permeability leading to large volume losses of intravascular fluid into the tissues, thereby decreasing the perfusion of the lungs, kidneys, and other organs[46].

In case of a severe pancreatitis, patients must be admitted in intensive critical care units where vital signs (pulse, blood pressure, and rate of breathing) and urine production can be monitored continuously[47]. Blood samples are repeatedly drawn to monitor hematocrit, glucose levels, electrolyte levels, white blood cell count, amylase and lipase levels.

Treatment of severe pancreatitis requires[48]:

- *aggressive fluid resuscitation* with electrolyte solutions in order to optimize cardiac index and maintain hemodynamic stability[11]. Swan-Ganz monitoring is helpful in such patients;
- *cardiovascular support* including maintenance of hematocrit around 30 for adequate microperfusion of the pancreas[24];
- *appropriate respiratory care* with supplemental oxygen and mechanical ventilation if requested;
- *liver and kidney support* with dialysis if necessary;
- *pain relief*[41];
- *enteral nutrition* via a nasojejunal or naso gastric tube has become the preferred route of feeding[49,50];
- *prophylactic antibiotics.* Bacterial infection occurs in 40-70% of patients with severe AP and this is a major cause of morbidity and mortality[7]. Mortality increases from 5-25% in patients with sterile necrosis to 15-28% when infection has occurred. Several controlled trials support the use of antibiotics who penetrate in the pancreatic parenchyma reducing the risk of intra-abdominal infections in patients with severe necrotizing AP[51]. Imipenem is shown to reduce septic complications[52] even if some authors prefer the use of metronidazole and levofloxacin. Unfortunately, fungal superinfection tends to develop later in the clinical course. Recently, the largest randomized placebo-controlled, double-blind trial[53] has been able to demonstrate that antibiotic prophylaxis with ciprofloxacin and metronidazole has no beneficial effects as regards the reduction of pancreatic infection and the decrease of hospital mortality. These data do not support antibiotic prophylaxis in all patients with necrotizing pancreatitis. Antibiotic therapy is only requested in specific subgroups of patients with pancreatic necrosis and a complicated course;
- *gut decontamination*[54]. There is no strong evidence in humans supporting the oropharyngeal and gastric decontamination with

Polymyxin E, Tobramycin, Amphotericin B and Cefuroxime because of the selection of resistant strains;
- *somatostatin* is a potent inhibitor of pancreatic secretion. Moreover, it blocks the release of cytokines and increases phagocytic activity of monocytes. Somatostatin shows also cytoprotective effects on pancreatic cells, but it is a potent splanchnic vasoconstrictor. Despite these data, some studies showed that Somatostatin does not improve the outcome in acute severe pancreatitis[55]. In conclusion, there is insufficient evidence to support the use of Somatostatin in moderate to severe acute pancreatitis. On the other hand, it's preventive potential on the development of acute pancreatitis after Endoscopic Retrograde Colangiography (ERCP) is well known;
- *protease inhibitors* are used to treat acute pancreatitis, but their effectiveness remains unclear. Treatment with protease inhibitors does not significantly reduce the mortality in patients with acute mild pancreatitis, but may reduce the mortality in patients with moderate to severe pancreatitis[56];
- the available evidence indicates that patients with severe acute pancreatitis do *not benefit from therapy with gastric antisecretory drugs*.

Endoscopic Treatment

The outcome of patients affected by gallstone pancreatitis is strictly correlated to the severity of the disease[57]. If it's true that most patients present with mild to moderate disease and recover quickly if submitted to conservative treatment[57,58], as stone(s) spontaneously pass into the duodenum[59], approximately 25% of these patients develop a severe pancreatitis, with a mortality rate that can reach the 25% in the presence of an infected pancreatic necrosis[60]. It's easy to understand that any procedure which can stop the fatal progression of the disease would be of great interest. Approximately 20 years ago, the first anecdotal reports of the application of ERCP and Endoscopic Sphincterotomy (ES) in the setting of acute biliary pancreatitis, documented the rapid improvement of the clinical picture after the biliary drainage[61]. The subsequent wide diffusion of this method allowed to evidence that about 70% of patients with biliary AP have stones in the common bile duct[62-66], thus enforcing the evidence of a pathogenesis due to biliary reflux in the main pancreatic duct and /or its transient obstruction[67-68]. Between 1988 and 1997, 4 randomized controlled trials tried to give an answer to the question of the correct timing of endoscopic approach of acute gallstone pancreatitis, comparing a group of patients submitted to early ERCP and ES to a control group which underwent only conservative treatment[62,69,70]. It is not easy to compare the results of these studies because of many differences as regards the timing of ERCP from the admission or the onset of symptoms, varying form 24 h[62,70] to 72 h[69,71], the criteria of severity assessment and the proportion of severe cases, the inclusion criteria, with special reference to patients affected by cholangitis or jaundice, the indication to ES, limited to patient with stones in the common bile duct[69-71] or to all patients randomized for endoscopic treatment[62], the study design, as regards to the number of centres included.

Despite these differences, a recent meta-analysis of the results of the above cited studies, showed significantly lower morbidity and mortality rates among patients submitted to early ERCP and ES than among those who underwent conservative treatment[72]. This was especially true in cases of gallstone pancreatitis assessed as severe[69,70] and if the procedure was performed within 24 h from the admission[70]. Only the study by Folsch et al[71] showed a worse outcome in patients submitted to ERCP and ES than in controls, but this trial was criticized for the following reasons: patients with cholangitis or jaundice, who were more likely to benefit from early endoscopic treatment, were excluded from the study; very few cases were classified as severe; the greatest part of the centres involved in the study treated an average of 2 patients per year, thus showing a very limited experience with ERCP and ES which can affect the safety and the efficacy of the procedure; Furthermore, the authors were not able to explain the high incidence of respiratory failure among patients who received early ERCP and ES[58].

In conclusion, we can affirm that ERCP and ES seem safe and effective in patients affected by severe biliary AP and should be

performed within 24 h from the admission. There is no evidence that the procedure modifies the history of the disease in cases of mild pancreatitis.

Surgery

In biliary pancreatitis the surgical procedure consists of removing the gallbladder and clearing out the ducts. Actually it represent the second line therapy if ERCP fails. In patients with infected pancreatic necrosis or haemorrhage or peritonitis, surgery is the only therapeutic choice, while in cases of sterile pancreatic necrosis unresponsive to intensive medical treatment is still under debate[73]. Occasionally, surgery is needed during the first few days of severe acute pancreatitis, for instance to clarify an uncertain diagnosis or to relieve an injury pancreatitis.

In conclusion, AP may range from a mild disease to a life-threatening condition. Rapid diagnosis through laboratory testing and radiologic studies is important to distinguish between mild or severe pancreatitis. The goals of medical management are to provide aggressive supportive care, decrease inflammation, limit infection or superinfection, and identify and treat complications as needed. In mild pancreatitis, pain usually resolves 24-48 hours after starting a regimen of no oral intake, narcotics for pain relief, and intravenous fluids. Patients with signs of severe disease at onset or patients showing clinical deterioration after hospital admission, should ideally be treated by a team of physicians qualified to care for critically ill patients. Severe pancreatitis, in fact, is often associated with a marked increase of microvascular permeability, leading to large volume losses of intravascular fluid into the tissues, thereby decreasing perfusion of the lungs, kidneys, and other organs. Vigorous hydration, cardiovascular and pulmonary support, pain relief, enteral nutrition and antibiotic prophylaxis are the main steps. ERCP and ES seem safe and effective in patients affected by severe biliary AP and should be performed within 24 h from the admission. Even with aggressive and appropriate care, necrotizing AP has a mortality rate of 40%.

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