JOP - Journal of the Pancreas 2000; 1(4):178-182

Assessments of Severity and Management of Acute Pancreatitis Based on the Santorini Consensus Conference Report

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Acute pancreatitis is a potentially lethal disease with varying widely in clinical features and severity which range from mild and self-limited to a rapidly progressive illness leading to multiple organ failure and death. The mortality rate ranges from 0% in the mild disease to 10% in sterile and 25% in infected pancreatic necrosis.

Thirty-one specialists in acute pancreatic disease from a wide range of disciplines such as anatomy, gastroenterology, internal medicine, pathology, radiology and surgery met in September 1997 to review the evidence concerning the diagnosis, the assessment of severity and the management of acute pancreatitis and to produce an agreed outcome statement which would be useful for medical professionals dealing with the care of individual patients [1].

Determination of pancreatic enzymes in serum remains the gold standard for the diagnosis of acute pancreatitis. Amylase and lipase are both enzymes released from the pancreas during the course of the disease. The plasma levels of both enzymes peak within the first 24 hours of symptoms, but the half life of amylase in plasma is shorter than that of lipase. An analysis of all the published series shows that lipase estimation has a slightly superior sensitivity and specificity and greater overall accuracy than amylase. This difference becomes more marked when there is a delay in the initial blood sampling. Although the difference in the performance of these two tests is small, it is definite [2].

It is accepted that ultrasonography does not have an important role in the diagnosis or staging of acute pancreatitis since, in the majority of cases, the examination is incomplete due to the presence of gas in the gut lumen, a result of a paralytic ileus which is usually present [3]. Early ultrasonography is however useful in the determination of gallstone aetiology, by demonstrating stones in the gallbladder or common bile duct dilatation.

In cases of a doubtful diagnosis, particularly with atypical presentation when abdominal pain is not a feature, or when hyperamylasaemia or hyperlipasaemia have been discovered unexpectedly, pancreatic imaging by computed tomography (CT) provides good evidence of the presence or absence of pancreatitis [4]. Diagnostic CT signs include pancreatic swelling, peri-pancreatic infiltrates, peri-pancreatic fluid collections and areas of non-enhancement of the pancreas.

Early identification of severely ill patients is helpful in ensuring rapid and appropriate treatment. Furthermore, recently, endoscopic sphincterotomy has become more widely used for the management of severe gallstone-induced acute pancreatitis and other specific therapies are available (e.g. antibiotic prophylaxis) or undergoing development (e.g. platelet activating factor antagonists). It seems likely that the earlier these treatments are applied, the more effective they will be in preventing complications. There is, therefore, a need for an early objective measure of severity.

In the 1970s, two systems were developed to assist in the categorization of patients with

acute pancreatitis. The system proposed by Ranson was complicated by the requirement for two separate systems dependent on alcohol or gallstone aetiology. The Glasgow System, and its subsequent modification, works well in all types of pancreatitis [5]. However, both these systems require 48 hours from admission for full assessment.

The advantage of APACHE II was that prediction using this system at 24 hours was as effective as the other scores at 48 hours [6]. The superiority of and earlier assessment with APACHE-II have been confirmed. If a multiple factor scoring system is to be used, the best choice at present appears to be APACHE II calculated at 24 hours.

Currently, the best prediction of an individual's risk of complications lies in the use of a number of factors, which have been shown independently to predict a severe outcome. These include clinical features, markers of pancreatic injury, and markers of the inflammatory response.

Obesity has been confirmed as a risk factor for serious complications, and in two of these, it was a useful marker of a fatal outcome [7]. There is a suggestion that intermediate obesity (body mass index, BMI, 25-30 Kg/m^2) predicts a lesser but nevertheless increased risk compared with normal body habitus. Obesity predicts a severe outcome independently of age and acute physiology. Obesity, as shown by a BMI gretaer than 30 Kg/m^2, is a reliable predictor of a severe outcome.

A number of studies have shown that a chest radiograph within 24 hours of admission can be useful for the prediction of complications. Pulmonary infiltrates or lung field opacities are, however, too observer dependent to be widely reliable. Two studies have indicated a significant association between pleural effusion seen on the early chest X-ray and subsequent complications or fatal outcome. While there is some increased risk with a right pleural effusion, the predictive value is maximal with left sided or bilateral effusions [8].

It seems likely that the appearance of necrosis becomes more clearly defined during the first 96 hours after admission. There is no published data to support the routine use of CT within the first 24 hours of admission, for diagnosing necrosis or predicting severity. Indeed, it seems likely that such a policy would lack sensitivity. CT is useful for diagnosing pancreatic necrosis, with close to 100% sensitivity between four and ten days.

Markers of pancreatic injury such as Phospholipase A_2, are good early markers of severe pancreatitis but they have no clinical application at present [9, 10].

The trypsin activation peptide (TAP) [11] and the carboxypeptidase B activation peptide (CAPAP) [12] show great promise as markers of severity. Further development is required for these assays to be clinically useful.

A number of markers are suitable for the urgent assessment of severity including interleukin-8 (IL-8) and IL-6 [13], tumor necrosis factor (TNF) and polymorphonuclear (PMN) elastase [14]. Because of their probable usefulness, the development of rapid tests suitable for clinical application is urgently required. C-reactive protein (CRP) becomes a good discriminator of severe and mild disease 48 hours after onset of symptoms [14]. A cut-off level of 150 mg/L is now accepted.

The management of acute pancreatitis must start as soon as possible with abundant fluid replacement and supportive care. Early restoration of circulating volume and arterial oxygen tension to normal values should reduce the risk of extensive necrosis and other complications. In order to achieve the best possible outcome for patients with acute pancreatitis, it is necessary to be referred to a specialized center for the management of their disease. This type of center should meet the following criteria:

- a large general hospital with a full range of principal medical and surgical specialities;
- surgeons, physicians, radiologists, intensivists, pathologists and microbiologists with specialized skills and experience in the management of severe acute pancreatitis;
- CT available 24 hours per day;

- endoscopists experienced with endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) available daily as a routine service, and at weekends and during holidays as an emergency service.

The value of prophylactic antibiotics in severe pancreatitis has been continuously debated upon for more than half a century. Results from recent controlled clinical trials suggest that there is probably a role for antibiotics in the prevention of complications [15] and probably for the reduction of mortality rates. There is also a large body of experimental evidence to support this conclusion and the observations that Gram negative bacteria are the most important with regard to prognosis and that they originate in the gut.

Almost all the recent studies have shown a significant reduction in infected necrosis and pancreatic abscess in the patients treated when compared to the controls. The mortality rate was reduced only in two trials. In particular, systemic antibiotics with selective gut decontamination reduced late mortality (more than 2 weeks from the onset of the disease) as a secondary effect to a decrease of Gram negative infection.

Regardless of the criticism that can be made of each of these clinical studies, taken together they indicate that prophylactic antibacterial treatment is strongly recommended in severe pancreatitis.

Appropriate antibiotics are those which are active against a wide variety of organisms in particular Gram negative pathogens. Antibacterial therapy should begin as early as possible after the identification of a severe attack [16].

Three studies have shown a significant reduction of complications and reduction of the mortality rate in those patients undergoing endoscopic treatment in comparison with those conventionally treated [17]. The fourth trial from Germany did not show any benefit from early ERCP and ES in gallstone pancreatitis, but this study excluded (and offered ERCP to all) patients with evidence of cholangitis or jaundice. These patients are most likely to have persisting bile duct stones and to benefit from endoscopic treatment.

Urgent endoscopic treatment is recommended for patients with severe forms of acute biliary pancreatitis and abnormal liver function, including patients with cholangitis. The timing of ERCP and ES should be as early as possible and no more than 72 hours from hospital admission.

Enteral feeding, started early in the course of severe acute pancreatitis is safe, theoretically attractive and probably reduces the risk of complications. Experience with nutritional support is needed and when enteral nutrition is administered in the early stages of severe acute pancreatitis, appropriate safeguards should be undertaken to ensure jejunal placement of the tube and to avoid vomiting and aspiration if ileus is present. There may be an important role for enteral nutrition in the postoperative management of patients undergoing operations for severe acute pancreatitis [18].

A wide variety of antiprotease and antisecretory agents, including aprotinin, glucagon, anticholinergics and fresh frozen plasma have no effect on severe acute pancreatitis. Modern antiprotease therapy (gabexate mesilate) and antisecretory therapy (somatostatin, octreotide) have no effect on mortality rates. Gabexate [19] and somatostatin [20] may have some effect in reducing complications, but the evidence is weak.

Given that the biology of acute pancreatitis is still not well understood, the rationale for surgical intervention is not easy to define. Moreover, surgical intervention itself is not always based on clear guidelines to which the clinician can refer.

Based on evidence, there is no reason to intervene in sterile necrosis [21, 22].

In some cases, when the diagnosis is uncertain and CT or magnetic resonance (MR) imaging are not available, an early laparotomy may be required and an operation is needed to establish the pathology of the intra-abdominal event. Early laparotomy and exposure of the pancreas may be helpful in a patient with rapid progression of multiple organ failure despite full intensive care.

Undoubtedly, the development of pancreatic parenchymal and/or extrapancreatic necrosis is the critical feature in determining the prognosis of and the need for surgery in acute pancreatitis [23]. Until now, the only absolute indication for surgical treatment (debridment) is clinical sepsis with proven (by fine needle aspiration) infection. There is no advantage in favor of any one particular surgical technique. There are many areas for future investigation concerning the diagnosis and management of acute pancreatitis. A number of controversies still exist such as the role of nutrition, the value of different individual tests in predicting severity and the clarification of the indications for surgical intervention. Therefore, the design of randomized trials will be of great importance in the near future.

Key words Amylases; Antibiotics; Body Mass Index; Enteral Nutrition; Gabexate (therapeutic use); Interleukins; Lipase; Obesity; Octreotide (therapeutic use); Pancreatitis, Acute Necrotizing; Phospholipases; Prognosis; Protease Inhibitors; Somatostatin (therapeutic use); Sphincterotomy, Endoscopic; Surgical Procedures, Operative; Tomography, X-Ray Computed; Ultrasonography

Abbreviations CAPAP: carboxypeptidase B activation peptide; ES: endoscopic sphincterotomy

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