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Acute pancreatitis – papers review

Ostre zapalenie trzustki – przegląd piśmiennictwa

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S u m m a r y

Acute pancreatitis (AP) is an acute nonbacterial inflammatory condition of the pancreas, with extremely different clinical expressions. It may occur as an isolated attack or may be recurrent. It has a variety of causes and can range in severity from mild to severe and life threatening. The diagnosis of acute pancreatitis requires at least 2 of the following: typical upper abdominal pain, serum levels of amylase or lipase > 3 times the upper limit of normal, and confirmatory findings from imaging analysis. So far, there has been no precise method for predicting the severity of AP, although in daily practice a number of criteria are being used. Optimal management of patients with acute pancreatitis, including fluid resuscitation, analgesia, antibiotics, nutrition, or surgical intervention when necessary, is essential in order to reduce mortality and morbidity associated with this disease.

S t r e s z c z e n i e

Ostre zapalenie trzustki (OZT) jest ostrą niebakteryjną chorobą zapalną trzustki, która przebiega z dużą różnorodnością postaci klinicznych. Może występować jako pojedynczy epizod bądź mieć charakter nawracający. OZT ma wiele czynników etiologicznych a jego przebieg może być od łagodnego przez ciężki do zagrażającego życiu. Diagnoza OZT wymaga minimum 2 z następujących: typowy ból w nadbrzuszu, podwyższenie poziomu amylazy lub lipazy w surowicy > 3 razy górna granica normy oraz potwierdzenia w badaniach obrazowych. Jak dotychczas, nie ma precyzyjnej metody prognozowania ciężkości OZT, aczkolwiek w praktyce klinicznej stosowane są różne kryteria. Optymalne leczenie pacjentów z OZT, obejmujące resuscytację płynową, leczenie przeciwbólowe, antybiotyki, żywienie czy interwencję chirurgiczną w odpowiednich przypadkach, jest kluczowe w celu zmniejszenia śmiertelności i chorobowości związanej z tą chorobą.

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Acute pancreatitis (AP) is defined as the acute nonbacterial inflammatory condition of the pancreas. It is derived from the early activation of digestive enzymes found inside the acinar cells, with variable compromise of the gland itself, nearby tissues and other organs. Although the disease process may be limited to pancreatic tissue, it also can involve peripancreatic tissues or more distant organ sites. AP is a disease with extremely different clinical expressions. It may occur as an isolated attack or may be recurrent (1). It has a variety of causes and can range in severity from mild to severe and life threatening. Most patients suffer a mild and limited disease but about one fifth of cases develop multiple organ disfunction syndrome (MODS), accompanied by high mortality (1). The correct diagnosis of acute pancreatitis should be made in all patients within 48 hours of admission. Mild acute pancreatitis has a very low mortality rate (less than 1 percent), whereas the death rate for severe acute pancreatitis can be 10 to 30 percent depending on the presence of sterile versus infected necrosis. This great variability in presentation, clinical course and complications has given rise to the confusion related to AP related terminology. However, consensus meetings (Atlanta and later working groups) have provided more uniform definitions. For the last 25 years, there has been a global increase in incidence of AP, along with many advances in diagnosis and treatment. This increase was associated

with a parallel increase in gallstone and alcohol-related pancreatitis.

Acute pancreatitis is a disease with an overall mortality of approximately 4-6% (which increases to 17-39% in severe disease) and substantive morbidity (2, 3). New mortality data in AP confirm that mortality rates are similar in gallstone and alcohol-induced AP, that mortality is 20% in those hospitalized more than 1month with severe AP (SAP), and that increased mortality occurred in those with hospital-acquired infection and those at least 70 years old (4).

The most common risk factors for acute pancreatic are gallbladder disease (often caused by choledocholithiasis) and chronic alcohol consumption. The etiology factors for acute pancreatitis are listed in table 1 (3, 5, 6). The etiology of acute pancreatitis should be determined in at least 80% of cases and no more than 20% should be classified as idiopathic (7).

Table 1. Etiology of acute pancreatitis (1).

Toxic – metabolic	Alcohol Hyperlipidemia, hypercalcemia Drugs and pills (azathioprine, didanosine, estrogen, furosemide, salicylates, sulfonamide, pentamidine) Organophosphorus and other toxic substances Venoms (scorpion, spiders)
Mechanical	Biliary: lithiasis, microlithiasis, sludge Congenital malformations Pancreas divisum Annular pancreas Anatomical variants: – Duodenal duplication – Duodenal diverticulum – Choledochal cyst Ampullary dysfunction and stenosis Trauma or post-procedure (ERCP, surgery)
Genetic	Familial Sporadic
Miscellanea	Vascular Hypotension Vasculitis Embolisms Hypercoagulability Autoimmune associated to other autoimmune disorders Sjögren syndrome Primary sclerosing cholangitis Celiac disease Autoimmune hepatitis Infections: – Virus: mumps, Coxsackie A, HIV, CMV – Bacteria: *Mycobacterium tuberculosis* – Parasites: Ascaris – Other: Mycoplasma Idiopathic

Cigarette smoking is an independent risk factor for AP and total exposure correlates with overall risk (4). Sex is strongly associated with the risk of acute pancreatitis: the incidence of alcoholic pancreatitis is higher in men, and the incidence of gallstone pancreatitis is higher in women. Multivariate analyses showed that acute pancreatitis was associated with a stone diameter of less than 5 mm and with mulberry-shaped gallstones.

CLINICAL PRESENTATION

The hallmark symptom of acute pancreatitis is the acute onset of persistent upper abdominal pain, usually with nausea and vomiting. The usual locations of the pain are the epigastric and periumbilical regions. The pain may radiate to the back, chest, flanks, and lower abdomen. Patients are usually restless and bend forward (the knee-chest position) in an effort to relieve the pain because the supine position may exacerbate the intensity of symptoms (5). Physical examination findings are variable but may include fever, hypotension, severe abdominal tenderness, guarding, respiratory distress, and abdominal distention. Accurate diagnosis is important because many other conditions have similar symptoms, including acute cholecystitis, choledocholithiasis, and penetrating duodenal ulcers. Potentially lifethreatening conditions to consider include a perforated viscus, an ischemic bowel, bowel obstruction, or myocardial infarction (6, 8).

Two types of pancreatitis were defined at the Atlanta symposium in 1992: one light form, usually auto limited; and the other severe, where local complications may appear, such as necrosis and distant organ failure (OF). Fortunately, these complications are uncommon, occurring in approximately 15% of the cases. The situation's severity will be determined by clinical, analytical and radiological criteria. Because some complications do not appear immediately (necrosis or pseudocysts), a severity definition will be made adequately at the end of the process (9).

DIAGNOSIS

Clinical features (abdominal pain and vomiting) together with elevation of plasma concentrations of pancreatic enzymes are the cornerstones of diagnosis. The diagnosis of acute pancreatitis requires at least 2 of the following: typical upper abdominal pain, serum levels of amylase or lipase > 3 times the upper limit of normal, and confirmatory findings from cross-sectional imaging analysis (10, 11). But there is no single laboratory or clinical sign which is pathognomonic for acute pancreatitis; many biomarkers and inflammatory mediators for predicting the severity of acute pancreatitis are being evaluated (5, 12).

The initial laboratory evaluation should include amylase and lipase levels, complete blood count with differential, metabolic panel (blood urea nitrogen, creatinine, glucose, and calcium levels), triglyceride level, urinalysis and arterial blood gases. Amylase and lipase, secreted by the acinar cells of the pancreas, are the most common laboratory markers used to establish the diagnosis of acute pancreatitis. Elevated amylase and lipase levels can be nonspecific, depending on the time since onset of pain, other intra-abdominal processes, and concomitant chronic diseases such as renal insufficiency. Pancreatic enzymes are released into the circulation during an acute attack. Levels peak early, and decline over 3-4 days. An important concept derives from this: the diagnosis of acute pancreatitis should not rely on arbitrary limits of values 3 or 4 times greater than normal, but values should be interpreted

in light of the time since the onset of abdominal pain (7). The half life of elevated amylase is shorter than that of lipase. Because it persists longer after the onset of the attack and because the pancreas is the only source of lipase, estimation of plasma lipase has slightly superior sensitivity and specificity and greater overall accuracy than amylase. Amylase levels may be normal in patients with alcoholism who present with acute pancreatitis, especially if they have had previous attacks of alcoholic pancreatitis; thus, serial testing may not be helpful. Plasma lipase is more sensitive and specific than plasma amylase. Recent research has examined potential biologic markers for predicting the severity and prognosis of pancreatitis. Trypsinogens and pancreatic protease involved in the autodigestive processes of acute pancreatitis appear promising. Other investigational serologic markers include trypsinogen activation peptide, C-reactive protein, procalcitonin, phospholipase A2, and the cytokines interleukin-6 and interleukin-8. Currently, these markers have limited clinical availability, but there is significant interest in better understanding markers of immune response and pancreatic injury because these could be valuable tools for reliably predicting the severity of acute pancreatitis (12, 13).

Plain radiographs contribute little to the diagnosis of acute pancreatitis. The recommended initial examination is ultrasonography. Ultrasound may show pancreatic swelling but the pancreas is visualised in only 25-50% of patients with acute pancreatitis. The value of ultrasonography lies in its ability to demonstrate gall bladder stones and dilatation of the common bile duct, as well as other pathology unrelated to the pancreas such as abdominal aortic aneurysm. The sensitivity of the US in the detection of gallstones is > 95% in uncomplicated cases; however in the setting of acute pancreatitis, sensitivity for gallstone detection is only 67-78% due to the ileus and bowel distension. Furthermore, sensitivity in the detection of common bile duct stones is between 25-90% (12, 14).

CT is occasionally indicated for diagnosis, if clinical and biochemical findings are inconclusive, especially when abdominal signs raise the possibility of an alternative abdominal emergency, such as a perforation or infarction of the bowel.

Liver biochemistry is helpful for the diagnosis of biliary pancreatitis. A meta-analysis found that a 3-fold increase of serum alanine transaminase (> 60 μ/l < 48 hours of symptoms) will identify gallstones as the cause in patients with pancreatitis with a positive predictive value of 95%. It should be kept in mind that around 10-15% of patients with biliary pancreatitis present with normal serum liver enzyme and bilirubin levels (14).

Contrast enhanced computed tomography must be performed > 72 h from onset of symptoms to allow delineation of the necrosis. Magnetic resonance imaging is also a reliable staging method with similar sensitivity and specificity to that of contrast enhanced computed tomography.

CLASSIFICATION

The revised Atlanta Classification recognizes 3 degrees of severity. Mild disease is defined as acute pancreatitis not associated with organ failure, local complications, or systemic complications. Most patients with mild acute pancreatitis do not require pancreatic imaging analysis and are usually discharged within 3 to 5 days of onset of illness. Moderately severe acute pancreatitis is defined by the presence of transient organ failure, local complications, or systemic complications. Transient organ failure is defined by organ failure that is present for < 48 hours. Patients with moderately severe acute pancreatitis frequently require extended hospitalization but have lower mortality rates than patients with severe acute pancreatitis. Severe acute pancreatitis is defined by the presence of persistent organ failure. Persistent organ failure is defined by organ failure that is present for > 48 hours. Most patients with persistent organ failure have pancreatic necrosis (8-10).

PREDICTION OF SEVERITY

There is agreement that there is still a need for an early objective measure of severity. So far, there has been no precise method for this purpose, although in daily practice, following several clinical guidelines, a number of criteria are being used.

Clinical examination in the first 24 hours of admission although specific lacks sensitivity and hence is unreliable and should be supported by objective measures. Immediate assessment should include clinical evaluation, particularly of any cardiovascular, respiratory, and renal compromise, body mass index, chest x ray. The presence of any organ failure should be documented. After 24 hours in hospital, clinical assessment and documentation of organ failure are required (tab. 2).

The Glasgow and Ranson scales have been and still are being used; they are easy to use, although they require 48 h for a complete evaluation. The Acute Physiology and Chronic Health Evaluation APACHE II scale and its modification for obese patients, is currently the most commonly used scale; a score higher than 8 indicates severe illness. The problem is that 14 variables must be recorded, but it can be useful to assess severity of illness at patient's admission. More recently, the bedside index for severity in AP system has been developed with a predictive value similar to APACHE II, but much simpler to implement because it only reflects five variables (tab. 3).

The authors identified five variables during the first 24 hours which predict in-hospital mortality based on a BISAP (contraction for the five variables) score of 0 to 5 (tab. 4): blood urea nitrogen (BUN) of greater than 25 mg/days, impaired mental status, systemic inflammatory response syndrome (SIRS), age of more than 60 years, or the presence of a pleural effusion. Mortality ranged from less than 1% (0 to 1 point) to as high as 26.7% (5 points). A Bedside Index of Severity in Acute Pancreatitis score > 2 within 24 hours is associated with a 7-fold increase in risk of organ failure and 10-fold increase in risk of mortality (4, 8, 15, 16).

Table 2. Features that may predict a severe attack, present within 48 hours of admission to hospital (7).

Initial assessment
Clinical impression of severity Body mass index > 30 Pleural effusion on chest radiograph APACHE II score > 8
24 h after admission
Clinical impression of severity APACHE II score > 8 Glasgow score 3 or more Persisting organ failure, especially if multiple C-reactive protein 150 mg/l
48 h after admission
Clinical impression of severity Glasgow score 3 or more C-reactive protein > 150 mg/l Persisting organ failure for 48 h Multiple or progressive organ failure

Table 3. Clinical Criteria Used in Prognostic Scoring Systems for Acute Pancreatitis (5).

APACHE II scale
Equation includes the following factors: age, rectal temperature, mean arterial pressure, heart rate, PaO_2, arterial pH, serum potassium, serum sodium, serum creatinine, hematocrit, white blood cell count, Glasgow Coma Scale score, chronic health status
CT Severity Index
CT grade A is normal pancreas (0 points) B is edematous pancreas (1 point) C is B plus mild extrapancreatic changes (2 points) D is severe extrapancreatic changes plus one fluid collection (3 points) E is multiple or extensive fluid collections (4 points) Necrosis score: None (0 points) > One third (2 points) < One third but less than one half (4 points) > One half (6 points) Scoring: CT grade + necrosis score
Imrie scoring system
Age > 55 years White blood cell count > 15 000 per mm^3 (15.0 × 109 per L) Blood glucose > 180 mg per dL (10 mmol per L) in patients without diabetes Serum lactate dehydrogenase > 600 U per L Serum AST or ALT > 100 U per L Serum calcium < 8 mg per dL PaO_2 < 60 mmHg Serum albumin < 3.2 g per dL (32 g per L) Serum urea > 45 mg per dL (16.0 mmol per L) Scoring: One point for each criterion met 48 hours after admission
Ranson's criteria
At admission or diagnosis: Age > 55 years White blood cell count > 16 000 per mm^3 (16.0 × 109 per L) Blood glucose > 200 mg per dL (11.1 mmol per L) Serum lactate dehydrogenase > 350 U per L AST > 250 U per L During initial 48 hours: Hematocrit decrease > 10 percent Blood urea nitrogen increase > 5 mg per dL (1.8 mmol per L) Serum calcium < 8 mg per dL (2 mmol per L) Base deficit > 4 mmol per L (4 mEq per L) Fluid sequestration > 6000 mL PaO_2 < 60 mmHg Scoring: One point for each criterion met

APACHE II – Acute Physiology and Chronic Health Evaluation; PaO_2 – partial arterial oxygen tension; CT – computed tomography; AST – aspartate transaminase; ALT – alanine transaminase

Table 4. The bedside index for severity in acute pancreatitis prognosis system (BISAP).

Parameters	
Blood urea nitrogen	BUN > 25 mg/dL
Impaired mental status	Conscious status impairment
Systemic inflammatory response	SIRS criteria presence*
Age	> 60 yrs
Pleural effusion	Pleural effusion at X ray

*Systemic inflammatory response syndrome – presence of ≥ 2 criteria: heart rate > 90 bpm; temperature > 38°C or < 36°C; respiratory rate > 20 bpm or $PaCO_2$ < 32 mmHg; leucocytes > 12 000 or < 4000 cells/mm^3 or > 10% immature forms
BUN – blood urea nitrogen

The presence of 2 or more of the following criteria is used to define SIRS: temperature > 38°C or < 36°C, pulse > 90 beats/min, respirations > 20 beats/min, and white blood cell count > 12 000 or < 4000 cells/mm^3 or > 10% immature (bands) forms. From a clinical standpoint, tracking a patient's SIRS status offers important prognostic information; 25 to 60% of patients have SIRS when they are admitted, but the disorder resolves in more than half of these patients within 24 hours when they are given appropriate fluid resuscitation. An increasing number of SIRS criteria during the initial 24 hours of hospitalization increases the risk of persistent organ failure and necrosis as well as mortality. Patients with persistent SIRS (beyond 48 hours) have 11 to 25% mortality (8, 11).

Prospective studies have shown that the level of BUN at admission and during the initial 24 hours of hospitalization is a strong prognostic factor. For example, patients with a level of BUN at admission > 20 mg/dL that increased during the initial 24 hours have 9 to 20% mortality. By contrast, patients with an increased level of BUN at admission that decreased at least 5 mg/dL within 24 hours have 0 to 3% mortality. A normal level of BUN at admission followed by even a modest increase (2 mg/dL) during the initial 24 hours is associated with a 6 to 15% risk of death (1, 8). By contrast, patients with a normal level of BUN at admission without a subsequent increase within 24 hours have less than 1% mortality. A serum level of creatinine > 1.8 mg/dL within the first 24 hours of hospitalization is associated with a 35-fold increased risk of development of pancreatic necrosis (8).

The C-reactive protein (CRP) is broadly recognized as an indicator of severity. Its serum peak appears 48 h after the disease onset and currently its precision as a prognostic factor is high. The Santorini consensus and the World Association guidelines recommend a cut off of 150 mg/l. Values higher than 150 mg/L have a sensitivity of 80%, specificity of 76%, PPV of 76% and NPV of 86%, as an indicator of severe AP, even when correlated with necrosis (1).

Marked hemoconcentration appears when a large amount of liquid has been accumulated in a third space. A prospective study showed that a hematocrit of 44%, together with the inability to decrease this level

in 24 h, were good predictors of MODS and indicators of pancreatic necrosis (1). Activation peptides of pancreatic enzymes, in particular trypsinogen activation peptide and carboxypeptidase activation peptide, have been shown to provide good prognostic information in acute pancreatitis. However, rapid assays suitable for clinical use are not yet available (17).

It is well known that a pleural effusion, seen in a chest X-ray on admission, predicts poor progress (12, 17). However, it is more important to focus on the abdominal computed tomography (CT) scan findings, mainly when intravenous contrast administration has been completed, which will show the existence of necrosis, a severe criteria in the Atlanta classification (12). A gradation system, used according to CT findings, was developed by Balthazar and has been broadly extended. This, together with a score depending on necrosis extension, allows the calculation of a radiological severity index (CT Severity Index). Patients with a score higher than 5 had higher mortality, longer hospital stays and required more necrosectomies.

Not all patients with the diagnosis of AP require an abdominal CT scan. This should be reserved for those with severe AP or that show an evident deterioration during their stay. If a CT is to be obtained, it will preferably be done between the fourth and tenth day after the disease onset. Classically, it used to be said that a very early CT was not very helpful, but for some authors its utility has been demonstrated in the first 36 h to 48 h. Contrast-enhanced CT is required for the accurate diagnosis of the presence and range of pancreatic necrosis (12, 14).

What is interesting, body mass index > 30 kg/m^2 increases the risk of severe pancreatitis 3-fold and mortality 2-fold (8).

TREATMENT

There is a growing body of evidence that early management of patients with acute pancreatitis may alter the natural course of disease and improve outcomes of patients. Optimal management of patients with acute pancreatitis is essential in order to reduce mortality and morbidity associated with this disease (7). The time limit for efficacious medical treatment is of no more than 60 hours from the onset of symptoms of acute pancreatitis. The treatment needs to be tailored to each individual patient and to the available resources of each Institution (18).

Fluid

Adequate prompt fluid resuscitation is crucial in the prevention of systemic complications (5, 19). Although the majority of patients will have mild disease that resolves spontaneously, it is difficult to detect patients at risk of complications early in the hospital admission. There is some evidence that early oxygen supplementation and fluid resuscitation may be associated with resolution of organ failure, and early resolution of organ failure is associated with very low mortality, so it is appropriate to ensure that all patients with acute pancreatitis receive adequate oxygen and fluids until it is clear that the danger of organ failure has passed.

Oxygen saturation should be measured continuously and supplemental oxygen should be administered to maintain an arterial saturation greater than 95% (1, 20).

Fluids are given intravenously (crystalloid or colloid as required) to maintain urine output > 0.5 ml/kg body weight. The amount and composition of fluids used for replacement is not standardized, but resuscitation must be aggressive from the beginning and the patient's response carefully monitored; urine output, hematocrit and BUN are used as an indirect measurement of hypovolemia, mainly in the first 12-24 h if they were elevated at the beginning (hematocrit > 44% and BUN > 20 mg/dL). In patients with a risk of fluid overload, it is necessary to monitor the central venous pressure or even to insert a pulmonary artery catheter (Swan-Ganz) to monitor the cardiac preload. It is wise to treat every patient aggressively until disease severity has been established (1). Calcium and potassium chloride should be replaced if deficiencies arise. Hyperglycemia is managed with insulin as needed (19).

A pitfall of aggressive volume resuscitation is the risk of inducing pulmonary edema/fluid overload. Underlying morbid conditions or clinical indicators of predicted severe AP may precipitate admission to an ICU for hemodynamic assessment (4).

A prospective, randomized, controlled trial assessed the effects of bolus infusion of 20 mL/kg in the emergency department, followed by continuous infusion of 3 mL/kg/h, with interval assessment every 6 to 8 hours (comprising vital sign monitoring, pulse oximetry, and physical examination). Repeat volume challenge was administered if the level of BUN did not decrease. Alternatively, if the BUN level decreased, the rate of the infusion was reduced to 1.5 mL/kg/h. This approach was found to be safe and feasible in an acute care setting. In general, patients undergoing volume resuscitation should have the head of the bed elevated, undergo continuous pulse oximetry, and receive supplemental oxygen.

Lactated Ringer's solution reduces the incidence of SIRS by > 80% compared with saline resuscitation, although these findings await further confirmation. Nevertheless, lactated Ringer's solution is a reasonable choice for initial resuscitation, based on its positive effects on acid-base homeostasis, compared with large-volume saline resuscitation (1, 8, 11).

Pain

Usually, abdominal pain is the main symptom in AP and its control is an essential goal of treatment. There is no evidence confirming the superiority of any analgesic. The treatment must be gradual and several drugs may be used, such as pirazolones (metamizol) or opioids (meperidine, morphine, tramadol), which are usually administered intravenously. Pump analgesia, instead of bolus, is a good option when the pain is intense. In patients with severe pain or difficult analgesic control with standard measures, the epidural administration of opioids or local anesthetics has been used with good results in terms of gas exchange and bowel

motility. Similarly, clinical trials using bupivacaine have shown the improvement of pancreatic microcirculation, together with a lower development of necrosis and systemic complications (1, 8, 19).

Antibiotics

The available studies are not individually conclusive although some have shown benefit from antibiotic prophylaxis (19). There remains no consensus view on the value of antibiotic prophylaxis (4, 9). If antibiotic prophylaxis is used, it seems sensible to limit the duration of prophylaxis to 7-14 days. Treatment should not be continued beyond that time without evidence of infection provided by bacterial growth on culture. When such evidence exists, appropriate antibiotic therapy should be guided by the results of sensitivity testing in accordance with critical care medicine guidelines (7).

According to expert opinion, prophylactic antibiotics may be considered to treat patients who have evidence of SIRS or failure of one or more organs, but this remains controversial and requires further study. Finally, antibiotics should be used when patients have evidence of sepsis or proven pancreatic or extrapancreatic infection (6, 15).

Nutrition

Patients with light AP generally respond to fluid replacement in a few days without any repercussions on nutritional status. Oral feeding is recommended when vomiting or ileus is not present. Occasionally, oral feeding may elicit pain and should be stopped. However, when pain remits, usually between 24-48 h after the onset, oral feeding should be resumed. Classically, a fluid diet is followed by low fat diet (below 30% of total calories), progressing to adequate (1, 6, 8).

The Santorini consensus and the World Association guidelines comment on five studies that demonstrate the safety of enteral feeding in patients with acute pancreatitis. There is no benefit from enteral feeding in mild pancreatitis, and these patients need have no dietary restrictions. It has been shown that EN, compared to TPN, is associated with a lower incidence of metabolic complications and infection, since the integrity of the intestinal barrier is kept. It allows also better glycemic control (4). On the other hand, EN is cheaper and requires a shorter hospital stay. Besides, EN avoids some mechanical and septic complications related to central venous catheters that may reduce mortality (21). This endpoint is clinically important because infectious complications are responsible for up to 50% of mortality in patients with severe AP. If required, nutritional support should be provided early in the course of AP, as soon as in the first 48 h. Once the severity of the disease has been assessed, it is preferable to use semi elemental formulas with high protein and low lipid content, increasing the amount according to tolerance. EN tolerance is variable and depends on the infusion's rate, nutrient's concentration, place of delivery (stomach, jejunum) and the phase of inflammatory response of AP. If the placement of a postduodenal tube is not possible, nasogastric tube may be used. The nasogastric route appears to be effective in 80% of cases (7, 22). In some patients, pain reappears and pancreatitis worsens, increasing the size of collections, when oral feeding is resumed or EN is set up. In these cases, TPN should be used.

There is a single study in pancreatitis where the objective is to assess the type of diet administered. This study includes a small number of seriously ill patients with pancreatitis, and concludes that both oligomeric and polymeric diets are well tolerated in patients with pancreatitis. There is theoretical tolerance advantage favorable to the semielemental diet, as it contains small peptides and middle-chain lipids, that do not require pancreatic enzymes to be digested, but, in the opinion of the experts, polymeric diets may be used safely (21, 22).

Others

Nasogastric suction is often used in patients with acute pancreatitis, even if most of the published studies limit this approach only to the patients with severe disease (18).

Gastric acid secretion inhibition is largely used in patients with acute pancreatitis, even if there are very few studies on this issue and the results are not conclusive (19).

There is no proven therapy for the treatment of acute pancreatitis. Despite initial encouraging results, antiproteases such as gabexate, antisecretory agents such as octreotide, and anti-inflammatory agents such as lexipafant have all proved disappointing in large randomised studies.

Gallstones

Urgent therapeutic ERCP should be performed in patients with acute pancreatitis of suspected or proven gallstone aetiology who satisfy the criteria for predicted or actual severe pancreatitis, or when there is cholangitis, jaundice, or a dilated common bile duct. The procedure is best carried out within the first 72 hours after the onset of pain (4). All patients undergoing early ERCP for severe gall stone pancreatitis require endoscopic sphincterotomy whether or not stones are found in the bile duct. Patients with signs of cholangitis require endoscopic sphincterotomy or duct drainage by stenting to ensure relief of biliary obstruction. All patients with biliary pancreatitis should undergo definitive management of gall stones during the same hospital admission, unless a clear plan has been made for definitive treatment within the next two weeks (11, 14, 23).

There is consensus that: (a) ERCP and endoscopic sphincterotomy are indicated within 24 hours in patients with acute biliary pancreatitis (ABP) with obstructive jaundice and/or acute cholangitis and (b) routine ERCP prior to cholecystectomy is not required in most patients with ABP and mild disease because bile duct stones typically pass spontaneously.

Necrosis

Because the features of the systemic inflammatory response syndrome are identical to those of sepsis, clinical parameters will not identify pancreatic infection

before it is too late. Thus from day 5-7 of a severe attack all patients must undergo a contrast enhanced computed tomography. If there is > 30% necrosis there should be weekly computed tomography-guided fine needle aspiration for bacteriology and fungi (FNAB) which has a sensitivity of 96% for detecting pancreatic infection (7). The indications for surgery in severe acute pancreatitis are now well defined: positive FNAB stain or culture or extra-intestinal gas on a contrast enhanced computed tomography scan are indications for necrosectomy. Other indications for surgery include sterile necrosis with persisting systemic or local symptoms despite 3-4 weeks of maximal conservative treatment (7). Surgery should be considered in all patients with: (a) multi-organ failure with necrosis that does not respond to conservative treatment; (b) compartmental syndrome (IAP > 25 mmHg) with persistent organ failure; (c) infected necrosis; and (d) mesenteric ischaemia and/or perforation of the intestine (20).

Necrosectomy must be delayed for at least 2-3 weeks to allow demarcation of the necrosis. In a recent study, necrosectomy was performed after a median of 31 days from disease onset (13). Conservative management of patients with sterile necrosis has a mortality rate of 1.8% while mortality in patients with infected necrosis who undergo surgery is 24-39%. There are three main techniques that can be used for necrosectomy: open necrosectomy with closed lesser sac lavage, repeated laparotomies with zipper to close the peritoneum after each intervention or left open as laparostomy and minimally invasive necrosectomy (10, 24). Surviving patients with severe disease should undergo cholecystectomy at a later stage (> 6 weeks) as there is increased morbidity and longer hospital stay if they have an early operation.

CHEMOPREVENTION OF POST-ERCP PANCREATITIS (PEP)

Several groups (re)examined chemoprevention therapy for PEP by randomized controlled trials (RCTs) and meta-analyses and reported inconclusive results for allopurinol, corticosteroids, unfractionated heparin, and intravenous nitroglycerin. One exception is that prophylactic rectal nonsteroidal anti-inflammatory drugs (indomethacin or diclofenac) may reduce PEP, based on data from RCTs and a meta-analysis of four RCTs. For unclear reasons, the route of drug delivery may have critical importance; oral diclofenac did not reduce PEP (4, 8).

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