

ACUTE BILLIARY PANCREATITIS - FROM DIAGNOSIS TO TREATMENT

Adrian Goldis, Iulia Ratiu

REZUMAT

Pancreatita acută apare de obicei ca rezultat al consumului de alcool sau al obstrucției biliare. Pancreatita acută biliară are de obicei o evoluție benignă la majoritatea pacienților. Totuși, în 20% din cazuri boala este severă și se asociază cu o mortalitate de până la 20%. Nivelul seric al lipazei este utilizat ca marker biologic de diagnostic. Deși nu se utilizează de rutină, tripsina serică este cel mai specific indicator al pancreatitei acute. Identificarea rapidă a pacienților critici utilizând scorurile de severitate este crucială pentru evoluția ulterioară a acestora. Utilizarea aspirației nazo-gastrice, administrarea de anticolinergice, antisecreterii nu au demonstrat o ameliorare a simptomatologiei sau o scădere a duratei de spitalizare a pacienților. ERCP de urgență se indică în formele severe de pancreatită acută biliară și în angiocolite.

ABSTRACT

Acute pancreatitis usually occurs as a result of alcohol abuse or bile duct obstruction. Acute biliary pancreatitis (ABP) is a common disease that normally runs a benign course in the majority of patients. However in up to 20% of individuals the disease is severe and may be associated with mortality close to 20%. Serum lipase level is still used to confirm the diagnosis of acute pancreatitis. Although not routinely available, the serum trypsin level is the most accurate laboratory indicator for pancreatitis. Prompt identification of patients who need intensive care referral or subspecialty consultation is crucial. Therapies such as nasogastric suctioning, anticholinergics and antisecretors have not been shown to decrease symptoms or hospital stays in patients with acute pancreatitis. Urgent ERCP is indicated in severe forms of acute biliary pancreatitis and suspicion of cholangitis.

Learning objectives: The aim of this review is to highlight the important aspects regarding acute biliary pancreatitis. After studying this article young doctors should be able to clearly appreciate the severity of pancreatitis and to establish the adequate management.

INTRODUCTION

From mild disease to multiorgan failure and sepsis, acute pancreatitis is a disorder that has numerous causes, an obscure pathogenesis, few effective remedies, and an often unpredictable outcome. In 1925, Moynihan aptly described the dramatic nature of acute pancreatitis as the “most terrible of all calamities that occur in connection with the abdominal viscera. The suddenness of its onset, the illimitable agony which accompanies it, and the mortality attendant upon it

render it the most formidable of catastrophes”.¹ Just over 100 years ago, Reginald Fitz described many of the modern clinical and pathologic features of severe acute pancreatitis.^{2,3} At the turn of the century, Opie brought to light the association between cholelithiasis and acute pancreatitis.⁴

Over the past decades several epidemiological studies have been published reporting on incidence trends, hospital admissions, etiological factors and outcome of both acute and chronic pancreatitis. Over time, the incidence of acute pancreatitis has increased in the Western countries. Also, the number of hospital admissions for both acute and chronic pancreatitis has increased. These upward time trends possibly reflect a change in the prevalence of main etiological factors (e.g. gallstones and alcohol consumption) and cofactors such as obesity and genetic susceptibility. Acute and chronic pancreatitis are associated with significant morbidity and mortality and a substantial use of health care resources. Although the case-fatality rate of acute pancreatitis decreased over time, the

Department of Gastroenterology, Clinical Emergency County Hospital, Timisoara

Correspondence to:
Assoc. Prof. Adrian Goldis, Department of Gastroenterology, Clinical Emergency County Hospital, 10 Dr. I. Bulbuca Blvd., Timisoara, Tel. +40-722-410712.
Email: goldisadi@yahoo.com

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overall population mortality did not change for both acute and chronic pancreatitis.⁵

The incidence is about 30-50/100,000/year.⁶ In 80% of cases the disease is associated with interstitial edema, mild infiltration with inflammatory cells and intra- or peripancreatic fat necrosis. Evolution is benign and self-limited with proper treatment. The severe form occurs less frequent (15-20%), results in long lasting hospitalization and is associated with high mortality (30-40%), due to infected necrosis and multiple organ failure.⁷ Alcoholism and biliary disease account for 80% of cases.

Rare etiologies of disease include metabolic factors (hypercalcemia, hyperlipoproteinemia, drug ingestion), obstructive factors (abdominal tumors, trauma, endoscopic retrograde cholecistopancreatography, etc.), infections (viral, parasitic) and hemodynamic factors. Postoperative pancreatitis is a complication after major abdominal surgery (abdominal aorta aneurism repair, extensive upper abdominal surgery, hepatic or cardiac transplant, etc.).

PATHOPHYSIOLOGY

The precise mechanism by which obstruction of the sphincter of Oddi by a gallstone or microlithiasis (sludge) causes pancreatitis is unclear, although it probably involves increased ductal pressure. Undoubtedly, this disease entity has numerous causes, an obscure physiopathology, few effective remedies, and, often, an unpredictable outcome. At the turn of the century, Opie brought to light the association between gallstone migration and acute pancreatitis.^{4,8}

When bile and/or pancreatic juice cannot reach the duodenal lumen, the entero-pancreatic feedback loop gets interrupted. This triggers the rising of blood's CCK levels, and, through the induction of an increased cytosolic Ca²⁺ concentration, a supramaximal stimulation of the pancreon's acinar cells is elicited.^{9,10} The foregoing is linked to the evoking of both positive and negative duodenopancreatic reflexes. Indeed, when in the duodenal lumen the influence normally exerted by bile, trypsin and chymotrypsin lessens (bile and/or pancreatic juice diversion bile and/or pancreatic duct obstruction) the releasing of CCK from the duodenal mucosa is markedly enhanced.

A neurotransmitter induced by the presence in the duodenal lumen of trypsin, chymotrypsin and/or bile, might be at the basis of restricting influences on the pancreon units. Acute pancreatitis may occur when factors involved in maintaining cellular homeostasis are out of balance. The mechanisms by which alcohol

or gallstones cause destruction to pancreatic acinar cells are not currently known.

Once a cellular injury pattern has been initiated, cellular membrane trafficking becomes chaotic, with the following deleterious effects: (1) lysosomal and zymogen granule compartments fuse, enabling activation of trypsinogen to trypsin; (2) intracellular trypsin triggers the entire zymogen activation cascade; and (3) secretory vesicles are extruded across the basolateral membrane into the interstitium, where molecular fragments act as chemoattractants for inflammatory cells. Activated neutrophils then exacerbate the problem by releasing superoxide (the respiratory burst) or proteolytic enzymes (cathepsins B, D, and G; collagenase; and elastase). Finally, macrophages release cytokines that further mediate local (and, in severe cases, systemic) inflammatory responses.

The early mediators defined to date are tumor necrosis factor- α , interleukin-6, and interleukin-8. These mediators of inflammation cause an increase pancreatic vascular permeability, leading to hemorrhage, edema, and eventually pancreatic necrosis. As the mediators are excreted into the circulation, systemic complications can arise, such as bacteriemia due to gut flora translocation, acute respiratory distress syndrome, pleural effusions, gastrointestinal hemorrhage, and renal failure. Eventually, the mediators of inflammation can become so overwhelming to the body that hemodynamic instability.

CLINICAL SIGNS

The cardinal symptom of acute pancreatitis is abdominal pain. Usually, the pain is sudden in onset and gradually intensifies in severity until reaching a constant ache. Most often, it is located in the upper abdomen, usually in the epigastric region, but it may be perceived more on the left or right side, depending on which portion of the pancreas is involved. 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. The supine position may exacerbate the intensity of symptoms because of the peritoneum elongation and the increased irritation of retroperitoneal structures by the pancreatic inflammation. After a few days the pain can migrate into the lower abdomen as an expression of the local fat necrosis determined by pancreatic juice leakage.

Nausea and vomiting are often present along with accompanying anorexia. The duration of pain

varies but typically lasts more than a day. It is the intensity and persistence of the pain that usually causes patients to seek medical attention. Nausea and vomiting are persisting, does not improve the pain and are never fecaloid. Nausea and vomiting has multiple explanations: The extension of pancreatic inflammation to the posterior gastric wall, liquid accumulation in omental bursa which presses the gastric corpus determining obstruction, acute gastric dilatation and the pain.

The following physical examination findings vary with the severity of the disease:

- The majority of patients exhibit jaundice-obstructive jaundice because of the choledoc lithiasis or Mirizzi syndrome, an unusual presentation of gallstones that, when lodged in either the cystic duct or the Hartmann pouch of the gallbladder (infundibulum), externally compressed the common hepatic duct.

- Abdominal tenderness, muscular guarding, and distension are observed in most patients. Bowel sounds are often hypoactive due to gastric and transverse colonic ileus. Guarding tends to be more pronounced in the upper abdomen. Ileus is explained by the inflammation extension to the mesentery and mesocolon and by chemical peritonitis. In acute pancreatitis we encounter a characteristic discrepancy between the complains and the barely objective signs in physical examination. Abdominal distension sometimes can appear due to pancreatic ascites, pseudocyst or pancreatic flegmon. Ascites results from principal pancreatic channel rupture, pseudocyst rupture or peritoneal exudation.

- Some patients experience dyspnea, which may be caused by irritation of the diaphragm (resulting from inflammation), pleural effusion, or a more serious condition, such as acute respiratory distress syndrome (ARDS). Pulmonary dysfunction ranging from hypoxemia to ARDS is one of the most important systemic manifestations of severe acute pancreatitis occurring in 30-50% of patients.^{11,12} Pulmonary dysfunction is the major factor of mortality in 22-25% and a contributing factor in an additional 30% of patients with acute pancreatitis.¹³ Oxygen saturation of 92% or below is reported to be an independent predictor of the severity of AP and is reported in 44% of patients with severe acute pancreatitis.¹⁴ Pulmonary infiltrates, pleural effusion and hypoxemia are markers of severe acute pancreatitis.¹³ A logistic regression analysis showed that radiological abnormalities of the chest were associated with a 15-fold increase in the mortality rate.¹⁵

- In severe cases, hemodynamic instability is

evident. In addition, patients with severe acute pancreatitis are often pale, diaphoretic, and listless. Pancreatic shock evokes severe disease forms. Peritoneal and retroperitoneal exudation, intrapancreatic and peripancreatic hemorrhage, fluid retention in perietic intestinal lumen are the main factors which contribute to the hypovolemic shock. In addition in shock genesis contributes the increased kinins and prostaglandins releasing with vasodilator effect and increasing vascular permeability. Moreover, the pancreatic enzymes gashing into blood system produces proteolysis and lipolysis and increasing vascular permeability.¹⁶

A few uncommon physical findings are associated with severe necrotizing pancreatitis:

- The Cullen sign is a bluish discoloration around the umbilicus resulting from hemoperitoneum.

- The Grey-Turner sign is a reddish-brown discoloration along the flanks resulting from retroperitoneal blood dissecting along tissue planes. More commonly, patients may have a ruddy erythema in the flanks secondary to extravasated pancreatic exudate.

- Erythematous skin nodules may result from focal subcutaneous fat necrosis. These are usually not more than 1 cm in size and are typically located on extensor skin surfaces. In addition, polyarthrititis is occasionally seen.

- Rarely, abnormalities on fundoscopic examination may be seen in severe pancreatitis. Termed Purtscher retinopathy, this ischemic injury to the retina appears to be caused by activation of complement and agglutination of blood cells within retinal vessels. It may cause temporary or permanent blindness.¹⁷

LABORATORY TESTS

Amylase and lipase

Amylase cannot be reabsorbed from intestine and normal amilasemia results from direct blood penetration and through lymph channels indirect amylase penetration from pancreatic acines and pancreatic or salivary ducts. Inflammation and obstruction at these levels determine the increasing of serum amylase levels. Amylase eliminates from serum by glomerular filtration and then, by renal tubular catabolization or urinary excretion. Urine amylase increased levels appear due to an increased glomerular filtration of serum amylase levels combined with a decreased tubular reabsorbtion.

Serum amylase and lipase levels are typically elevated in persons with acute pancreatitis. However,

these elevations may only indicate pancreastasis. In research studies, amylase or lipase levels at least three times above the reference range are generally considered diagnostic of acute pancreatitis.

Serum amylase determinations are routinely available, but they are not specific for pancreatitis. Elevations can occur in anyone with small intestinal obstruction, mesenteric ischemia, tubo-ovarian disease, renal insufficiency, or macroamylasemia. Rarely, elevations may reflect parotiditis.

The serum half-life of amylase is short, and elevations generally return to reference ranges within a few days.

Lipase has a slightly longer half-life and abnormalities may support the diagnosis if a delay occurs between the pain episode and the time the patient seeks medical attention. Elevated lipase levels are more specific to the pancreas than amylase levels.

The level of serum amylase or lipase does not indicate whether the disease is mild, moderate, or severe, and monitoring levels serially during the course of hospitalization does not offer insight into prognosis.¹⁸

There is general acceptance that a diagnosis of acute pancreatitis requires two of the following three features: 1) abdominal pain characteristic of acute pancreatitis, 2) serum lipase \geq 3 times the upper limit of normal, and 3) characteristic findings of acute pancreatitis on CT scan. This definition allows for the possibility that an amylase and/or lipase might be less than three times the upper limit of normal in acute pancreatitis. In a patient with abdominal pain characteristic of acute pancreatitis and serum enzyme levels that are lower than three times the upper limit of normal, a CT scan must be performed to confirm a diagnosis of acute pancreatitis. In addition, this definition allows for the possibility that presence of abdominal pain cannot be assessed in some patients with severely altered mental status due to acute or chronic illness.¹⁹

Enzymes: alkaline phosphatase, total bilirubin, aspartate aminotransferase, and alanine aminotransferase levels allow us to search for evidence of gallstone pancreatitis.

Calcium levels help the search for complications of pancreatitis (hypocalcemia resulting from saponification of fats in the retroperitoneum). Serum electrolytes, BUN, creatinine, and glucose: measure these to look for electrolyte imbalances, renal insufficiency, and pancreatic endocrine dysfunction.

CBC count: hemoconcentration at admission (an admission hematocrit value greater than 47%) has

been proposed as a sensitive measure of more severe disease. However, this has subsequently been shown to have value only as a negative predictor, that is, a lack of hemoconcentration effectively rules out severe disease. Leukocytosis may represent inflammation or infection.

C-reactive protein (CRP) value can be obtained 24-48 hours after presentation as an indicator of prognosis. A CRP value $>$ 150mg/dL strongly indicates severe pancreatitis. CRP is an acute-phase reactant that is not specific for pancreatitis.

Arterial blood gases: we have to measure them if a patient is dyspneic for determining whether tachypnea is due to acute respiratory distress syndrome or diaphragmatic irritation.

Trypsin and its precursor **trypsinogen-2** in both the urine and the peritoneal fluid have been evaluated as possible markers for acute pancreatitis but are not widely used. Trypsinogen activation peptide (TAP) is formed when trypsinogen is cleaved to form trypsin and can be measured commercially in the urine to diagnose acute pancreatitis and to help determine severity.

Although not currently in use clinically, polymorphisms in the chemokine **monocyte chemoattractant protein 1 (MCP-1)** gene may also predict severity. This is the first gene identified that plays a role strictly in predicting the severity of disease.

PARACLINICAL TESTS

Abdominal radiography has a limited role in acute pancreatitis, is used to detect free air in the abdomen for differential diagnosis with perforated ulcer. The inflammatory process may damage peripancreatic structures, resulting a sentinel loop, or an ileus.

Chest X-Ray films may show a spectrum of changes depending on the disease severity. A pleural effusion is the commonest finding, although in severe cases diffuse alveolar interstitial shadowing may suggest an acute respiratory distress syndrome (ARDS).

Ultrasound examination of the abdomen may be helpful in confirming the diagnosis. A swollen pancreas may be detected, but the gland is poorly visualized in 25-30% of cases, so this method cannot be used for definitive diagnosis.⁹ Ultrasound is valuable in detecting free peritoneal fluid, gallstones and dilatation of the bile ducts. Ultrasound is recommended initially in all patients with suspected acute biliary pancreatitis, is noninvasive and not expensive and may be repeated as frequently as clinical conditions dictate. An early diagnosis of gallstones is particularly important in

patients thought to have severe pancreatitis as the need for an urgent ERCP would then have to be considered. This is the most useful initial test in determining the etiology of pancreatitis and is the technique of choice for detecting gallstones. The ability to identify choledocholithiasis is limited. Ultrasonography cannot appreciate the severity of disease.

Abdominal CT scanning is not indicated for all patients being reserved for unclear cases, severe forms and complication.⁹ The distinction between interstitial and necrotizing pancreatitis can be made much more readily when a contrast-enhanced CT scan is obtained on the second or third day after admission rather than at the time of admission.²⁰ Additional contrast-enhanced CT scans may be required at intervals during the hospitalization to detect and monitor the course of intra-abdominal complications of acute pancreatitis, such as the development of organized necrosis, pseudocysts, and vascular complications. Contrast-enhanced CT scan (and in particular contrast enhanced thin-section multidetector-row CT scan) is the best available test to distinguish interstitial from necrotizing pancreatitis. When there is significant renal impairment (generally a creatinine greater than 1.5 mg/dL) or history of significant allergy to contrast dye, CT scan should be performed without the use of i.v. contrast. Although the distinction between interstitial and necrotizing pancreatitis cannot be made in the absence of contrast enhancement, a nonenhanced CT scan provides some important information in accordance with Balthazar–Ranson criteria for severity.

A healthy pancreas shows density numbers of 30–40 Hounsfield units on an unenhanced study, increasing to 100–150 Hounsfield units on an enhanced study. When pancreatic necrosis is present, focal or diffuse areas of unenhanced parenchyma on the second study suggest pancreatic necrosis. Pancreatic necrosis for research purposes is defined as loss of enhancement in at least 30% of the pancreatic parenchyma.²¹

Complications in acute pancreatitis that can be recognized on abdominal CT scan include pancreatic fluid collections, gastrointestinal and biliary complications (such as obstruction of duodenum or stomach, inflammation of the transverse colon, and biliary obstruction), solid organ involvement (such as splenic infarct), vascular complications (such as pseudoaneurysms, splenic vein thrombosis with varices, portal vein thrombosis), and pancreatic ascites.^{22,23}

Magnetic resonance imaging has not been widely used in the care of patients with acute pancreatitis. Recent reports have indicated that MRI has some advantages: the lack of nephrotoxicity of gadolinium as compared to an iodinated preparation used for contrast-enhanced CT scan, noradiation exposure, the greater ability of MRI as compared to CT to distinguish necrosis from fluid, and the overall reliability of MRI as compared to CT scan in staging the severity of acute pancreatitis and its complications.^{24,25} Disadvantages: the lack of availability when urgently needed, variation in quality among centers, and costs.

Table 1. The Balthazar score.

Element	Finding	Points
Grade of acute pancreatitis	Normal pancreas	0
	Pancreatic enlargement	1
	Inflammation involving pancreas and peripancreatic fat	2
	Single fluid collection or phlegmon	3
	Two or more fluid collections or phlegmons	4
Degree of pancreatic necrosis	No necrosis	0
	Necrosis of one third of pancreas	2
	Necrosis of one half of the pancreas	4
	Necrosis of more than one half of the pancreas	6

CT severity index = (points for grade of acute pancreatitis) + (points for degree of pancreatic necrosis)
 Interpretation: minimum score = 0; maximum score = 10

Severity index	Mortality	Complications
0-1	0%	0%
2-3	3%	8%
4-6	6%	35%
7-10	17%	92%

Endoscopic ultrasonography (EUS) is an endoscopic procedure that allows a high frequency ultrasound transducer to be inserted into the gastrointestinal tract to visualize the pancreas and the biliary tract. This study allows a more detailed image to be obtained than with transcutaneous ultrasonography because the high-frequency transducer can be introduced directly adjacent to the pancreas. EUS is often helpful in evaluating the cause of severe pancreatitis, particularly microlithiasis and biliary sludge.

Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic procedure used to evaluate the biliary and pancreatic ductal system. However, ERCP should be used with extreme caution in patients with acute pancreatitis and should never be used as a first-line diagnostic tool. ERCP is indicated for clearance of bile duct stones in patients with severe pancreatitis, in those with cholangitis, in those who are poor candidates for cholecystectomy, in those who are postcholecystectomy, and in those with strong evidence of persistent biliary obstruction. ERCP should be performed primarily in patients with high suspicion of bile duct stones when therapy is indicated. Routine ERCP should be avoided as a routine in patients who are planned to have cholecystectomy. EUS or Magnetic resonance cholangiopancreatography MRCP can be used to identify common bile duct stones and determine need for ERCP in clinically ambiguous situations.¹⁹

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute pancreatitis includes:

- Mesenteric ischemia or infarction;
- Perforated gastric or duodenal ulcer;
- Biliary or renal colic;
- Dissecting aortic aneurysm;
- Intestinal obstruction;
- Inferior wall myocardial infarction.

SEVERITY ASSESMENT

Risk factors of severity at admission:

- Older age (>55);
- obesity (BMI >30);
- Organ failure at admission;
- Pleural effusion and/or infiltrates.

Risk factors of severity at 48 h:

- Clinical impression of severity;
- Ranson score >3;

- APACHE score > 8;
- CRP > 150 UI/ml;
- Organ failure.

Risk factors of severity at 72 h:

- Clinical impression of severity;
- Ranson score > 3;
- APACHE score > 8;
- Maintaining organ failure or MSOF;
- CRP > 150 UI/ml.

Atlanta Severity Criteria:

- Ranson score > 3;
- APACHE score >8;
- Organ failure;
- Local complications: necrosis, abscess, pseudocyst.

Patients with these characteristics may require treatment in a highly supervised area, such as a step-down unit or an intensive care unit.^{19,26-32}

Table 2. The Ranson score.

Present on Admission:	Developing During the First 48 Hours:
Age > 55 years	Hematocrit fall > 10%
WBC > 16,000/ul	BUN increase > 8 mg/dl
Blood glucose > 200 mg/dl	Serum calcium < 8 mg/dl
Serum LDH > 350 I.U./L	Arterial oxygen saturation < 60 mm Hg
SGOT (AST) > 250 I.U./L	Base deficit > 4 mEq/L
	Estimated fluid sequestration > 600 ml

Ranson score of 0 - 2: minimal mortality;

Ranson score of 3 - 5: 10% - 20% mortality;

Ranson score > 5: more than 50% mortality, associated with more systemic complications.

The **APACHE II score** is given by the sum of the acute physiology score, the age (in years) points, and the chronic health points.²⁷ (Table 3)

Chronic Health Points

If the patient has a history of severe organ system insufficiency or is immunocompromised as defined below, we assign points as follows:

- 5 points for nonoperative or emergency postoperative patients;
- 2 points for elective postoperative patients.

Definitions: organ insufficiency or immunocompromised state must have been evident prior to this hospital admission and conform to the following criteria:

- Liver: biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior

Table 3. The APACHE II Severity of Disease Classification System.

Physiologic Variable	High Abnormal Range					Low Abnormal Range					Points
	+4	+3	+2	+1	0	+1	+2	+3	+4		
Temperature - rectal (°C)	≥ 41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤ 29.9		
Mean Arterial Pressure - mm Hg	≥160	130-159	110-129		70-109		50-69		≤ 49		
Heart Rate (ventricular response)	≥180	140-179	110-139		70-109		55-69	40-54	≤ 39		
Respiratory Rate (non-ventilated or ventilated)	≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5		
Oxygenation: A-aDO ₂ or PaO ₂ (mm Hg) a. FIO ₂ ≥0.5 record A-aDO ₂ b. FIO ₂ <0.5 record PaO ₂	≥500	350-499	200-349		< 200 PO ₂ >70	PO ₂ 61- 70		PO ₂ 55-60	PO ₂ <55		
Arterial pH (preferred) Serum HCO ₃ (venous mEq/l) (not preferred, but may use if no ABGs)	≥7.7 ≥52	7.6-7.69 41-51.9		7.5-7.59 32-40.9	7.33-7.49 22-31.9		7.25-7.32 18-21.9	7.15-7.24 15-17.9	<7.15 <15		
Serum Sodium (mEq/l)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110		
Serum Potassium (mEq/l)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5		
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6				
Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20		
White Blood Count (total/mm ³) (in 1000s)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1		
Glasgow Coma Score (GCS) Score = 15 minus actual GCS											
A. Total Acute Physiology Score (sum of 12 above points)											
B. Age points (years) ≤44 = 0; 45 to 54 = 2; 55 to 64 = 3; 65 to 74 = 5; ≥75 = 6											
C. Chronic Health Points (see below)											
Total APACHE II Score (add together the points from A+B+C)											

Table 4. Interpretation of Chronic Health Points score

Score	Death Rate (%)
0-4	4
5-9	8
10-14	15
15-19	25
20-24	40
25-29	55
30-34	75
>34	85

episodes of hepatic failure/encephalopathy/coma;

- Cardiovascular: New York Heart Association Class IV heart failure;

- Respiratory: chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction (i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hyper-

tension (> 40 mm Hg), or respirator dependency;

- Renal: receiving chronic dialysis;

- Immunocompromised: the patient has received therapy that suppresses resistance to infection (e.g., immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS).

TREATMENT

The majority of patients with acute biliary pancreatitis have mild disease while 15–30% develop severe pancreatitis.²⁶ Although only the latter suffer significant morbidity and mortality, it is wise to treat every patient aggressively until disease severity has been established.

The goals of acute pancreatitis management are:

1. Resuscitation: fluid replacement and electrolyte balance,
2. Symptomatic treatment: pain control and

nutritional support,

3. Prevention of local and systemic complications.

Any patient who has severe pancreatitis or significant comorbid medical conditions should be managed in a hospital with critical care facilities. According to the British Society of Gastroenterology a specialized center should be characterized by:

- A hospital, which has all of the principle medical and surgical specialities;

- The presence of a multidisciplinary team consisting of gastroenterologists, surgeons, intensive care doctors, endoscopists, radiologists and pathologists;

- The full-time availability of CT and US with personnel expert in invasive procedures.

- MRI and angiography can be helpful but are not strictly necessary.^{8,32}

Resuscitation

Transudation of fluid from the intravascular space to the peritoneum is the principle cause of hypovolemia in AP. Balanced electrolyte solutions (9% saline or Ringer's lactate) should be given promptly and the rate titrated to frequent assessment of the patient's volume status determined by heart rate, blood pressure, urine output and jugular venous pressure. Following rapid administration of crystalloid solution to correct the volume deficit, an infusion rate should be set that accounts for basal fluid requirements (35 ml/kg per day).³³ Adequate and prompt fluid resuscitation is crucial in preventing the systemic complications of the disease. This should be achieved within a few hours of presentation. If the volume status remains depleted despite these measures or if fluid administration is limited by respiratory decompensation, transfer to an intensive care unit for invasive monitoring and ongoing management is needed. For patients with severe pancreatitis or those with underlying cardiopulmonary disease, a central venous catheter and occasionally a pulmonary venous catheter may, in conjunction with transfer to an intensive care unit, be required.^{8,33}

Laboratory evaluation of renal function, electrolytes, glucose, hematocrit and arterial pH are useful adjuncts to the clinical evaluation. Glucose levels greater than 250 mg/dL necessitate insulin administration. A blood transfusion is indicated if the patient's hematocrit is less than 25%; values ranging from 30 to 35% are considered optimal for pancreatic parenchymal perfusion. Oxygen saturation should be measured continuously and supplemental oxygen to maintain an arterial saturation greater than 95%. Any evidence of respiratory insufficiency requires a chest X-Ray to assess for pulmonary edema or acute

respiratory distress syndrome (ARDS).^{32,33}

If vomiting occurs, an abdominal X-Ray should be performed to assess for ileus and a nasogastric tube inserted for gastric aspiration. The nasogastric tube is not indicated routinely because all recent studies have demonstrated that nasogastric aspiration does not improve the evolution of pancreatitis.^{9,32,33} Moreover, because of the mucosal irritation, gastric ulceration and upper digestive bleeding can appear.

Management of the pain

It is important to relieve abdominal pain with a parenterally administered narcotic medication. There is no evidence to suggest an advantage of any particular type of medication.

The amount of narcotic agent and the frequency of administration should be monitored closely by experienced physicians. Many hospitals have a dedicated pain service staffed by experienced physicians. When abdominal pain is particularly severe, patient-controlled analgesia can be used. It is particularly important to obtain measurements of bedside oxygen saturation frequently whenever narcotic agents are administered to relieve pain.⁹

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.^{9,33}

Nutritional support

Acute pancreatitis is a hypercatabolic state resulting in rapid loss of body weight, fat and protein. Nutritional support is an integral part of patient care and is started early in the course of disease. Whenever possible, enteral feeding rather than total parenteral nutrition (TPN) is suggested for patients who require nutritional support. In mild pancreatitis, oral intake is usually restored within 3-7 days of hospitalization, and nutritional support is not required.¹⁹ In severe pancreatitis, nutritional support should be initiated when it becomes clear that the patient will not be able to consume nourishment by mouth for several weeks. This assessment can usually be made within the first 3-4 days of illness. There is reason to believe that enteral feeding is preferable to TPN. First, there is compelling evidence that in severe acute pancreatitis gut barrier function is compromised resulting in greater intestinal permeability to bacteria (which may lead to infected necrosis) and endotoxins (which stimulate nitric oxide and cytokine production that contribute to organ

failure).³²⁻³⁴ There is also evidence that there is a higher incidence of gastric colonization with potentially pathogenic enteric bacteria in severe disease that may also contribute to septic complications.³⁵⁻³⁷

Use of prophylactic antibiotics in necrotizing pancreatitis

The use of prophylactic antibiotics to prevent pancreatic infection is not recommended at this time among patients with necrotizing pancreatitis.³³ Recently, a multicenter, double-blind, placebo-controlled study on the effectiveness of ciprofloxacin and metronidazole in reducing morbidity and mortality concluded that there was no difference in the rate of infected necrosis, systemic complications, or mortality in the two groups.³⁸ Using prophylactic antibiotherapy may lead to a superimposed fungal infection. This risk appears to correlate with prolonged use of antibiotic therapy.³⁹ There is no indication for routine antibiotics in patients with interstitial pancreatitis. During the first 7–10 days, patients with pancreatic necrosis may appear septic with leukocytosis, fever, and/or organ failure and antibiotic therapy is appropriate. If blood culture and culture of CT-guided fine needle aspiration are negative is recommended to discontinue antibiotic therapy.

Endoscopic treatment of acute biliary pancreatitis

In addition to supportive care, common to all types of acute pancreatitis, early endoscopic therapy has become increasingly integrated into the treatment for acute biliary pancreatitis over the last decade. Early endoscopic retrograde cholangiopancreatography reduces pancreatitis-related complications in patients with predicted severe pancreatitis although mortality rate is not affected. In predicted mild pancreatitis early endoscopic retrograde cholangiopancreatography has no advantage compared to conservative management.⁴⁰ The support for use of ERCP came from observational reports and randomized trials.^{40,41} The landmark of ERCP began in 1983 after sporadic case reports from various centers around the world reported rapid improvement of patients after establishment of biliary drainage and normalization of laboratory values. During the course of biliary pancreatitis, progressive increases in serum bilirubin and other liver function tests and persistent dilatation of the common bile duct are strongly suggestive of common bile duct obstruction by gallstones. In this circumstance, it is reasonable to proceed directly to ERCP. In clinical practice, if there is intermediate concern regarding the possibility of a retained common bile duct stone,

and the patient is not felt to be a good candidate for cholecystectomy with cholangiogram within the near future, EUS or MRCP can be performed to assess for presence of bile duct stones and determine need for ERCP.⁴¹

EUS is generally considered to be the most accurate method to detect bile duct stones; sensitivity of MRCP for small bile duct stones is lower, especially for those that are impacted at the ampulla.^{41,42} EUS or MRCP are also useful to determine need for ERCP in patients who are pregnant, or in whom ERCP would be high risk or technically difficult due to reasons such as severe coagulopathy or altered surgical anatomy.

All patients with biliary pancreatitis should undergo cholecystectomy during the same hospital admission or within the next two weeks

Table 5. Suggested indications for ERCP, EUS, and MRCP in patients with acute biliary pancreatitis.

Urgent ERCP (Preferably Within 24 h of Admission):

- Severe pancreatitis (organ failure)
- Suspicion of cholangitis

Elective ERCP with Sphincterotomy:

- Imaging study demonstrating persistent common bile duct stone
- Evolving evidence of biliary obstruction (such as rising liver chemistries)
- Poor surgical candidate for laparoscopic cholecystectomy
- Strong suspicion of bile duct stones postcholecystectomy

Endoscopic Ultrasound or MRCP to Determine Need for ERCP:

- Clinical course not improving sufficiently to allow timely laparoscopic cholecystectomy and intraoperative cholangiogram
 - Pregnant patient
 - High-risk or difficult ERCP (*e.g.*, coagulopathy, altered surgical anatomy)
 - Uncertainty regarding biliary etiology of pancreatitis
-

Treatment of necrosis

Sterile necrosis is best managed medically during the first 2–3 wk. After this interval, if abdominal pain persists and prevents oral intake, debridement should be considered. This is usually accomplished surgically, but percutaneous or endoscopic debridement is a reasonable choice in selected circumstances with the appropriate expertise.⁴⁴ All patients with persistent symptoms and greater than 30% pancreatic necrosis, and those with smaller areas of necrosis and clinical suspicion of sepsis, should undergo image guided fine needle aspiration with Gram's stain and culture 7-14 days after the onset of the pancreatitis. The technique of percutaneous aspiration has proven to be safe and accurate in distinguishing sterile from infected necrosis, except possibly during the first week of illness.^{44,45}

Figure 1. Algorithm for the evaluation and management of acute pancreatitis.⁵¹

Subjective	Acute onset steady, intense epigastric pain radiating to right and left upper quadrants, may be relieved with leaning forward, nausea and vomiting History of gallstones														
Objective	Mild: restlessness, low-grade fever, tachycardia, mild epigastric tenderness Severe: marked tenderness with guarding and abdominal distension, absent bowel sounds, hypotension, possible shock, pulmonary findings Laboratory tests: elevated pancreatic enzymes, bilirubin, liver function tests, cholestasys, consider complete blood count, arterial blood gases, glucose Imaging: ultrasound examination, contrast-enhanced CT or MRI in necrosis suspicion and severe cases, ERCP, MRCP in unclear cases														
Differential diagnosis	Gallstone disease, ulcerous disease, perforated ulcer, early appendicitis, mesenteric ischemia, bowel obstruction, traumatic injury, medication, acute alcohol consumption, pulmonary, renal or cardiac disorders, hypertriglyceridemia, hypercalcemia, acute porphyria, medications														
Assessment	<table border="1"> <thead> <tr> <th></th> <th>Ranson</th> <th>APACHE II</th> <th>CT severity Index</th> </tr> </thead> <tbody> <tr> <td>Mild</td> <td>< 3</td> <td>< 8</td> <td>< 7</td> </tr> <tr> <td>Severe</td> <td>> 3</td> <td>> 8</td> <td>> 7</td> </tr> </tbody> </table>		Ranson	APACHE II	CT severity Index	Mild	< 3	< 8	< 7	Severe	> 3	> 8	> 7		
	Ranson	APACHE II	CT severity Index												
Mild	< 3	< 8	< 7												
Severe	> 3	> 8	> 7												
Plan	Mild pancreatitis <ul style="list-style-type: none"> • Aggressive rehydration • Pain relief • Oral intake once pain improves • Clinical and paraclinical monitoring 	Severe pancreatitis <ul style="list-style-type: none"> • Consider intensive care unit admission • Aggressive volume replacement • Nutritional support (enteral feeding preferable) • Pain relief (morphine if necessary) • Consider emergent ERCP • Necrosis identification (contrast-enhanced CT) • Antibiotics in infection is present 													

In Gram-negative organisms, choices for antibiotic treatment include a carbipenem or a third generation cephalosporin, a fluoroquinolone plus metronidazole, pending results of culture and sensitivity. If Gram's stain reveals the presence of Gram-positive bacteria, a reasonable choice is vancomycin until results of culture and sensitivity are determined.^{44,45} Patients with infected necrosis will require intervention to completely debride all cavities containing necrotic material.

Local complications of pancreatic necrosis, such as pseudocyst and pancreatic abscess, often require surgical or endoscopic intervention. Reported results of surgical and endoscopic drainage are similar and percutaneous techniques may be successful in appropriate cases. Each case should be managed in an individualised way, by a multidisciplinary specialist pancreatic team, taking account of these features. Where severe compression effects are occurring, decompression may be necessary in a fairly urgent manner with optimum results being obtained by internal drainage which can be afforded by endoscopic stent placement in a long disrupted pancreatic duct or directly placing the stent into the pseudocyst through the wall of the stomach or duodenum.

Alternative therapy includes either open or laparo-

scopic surgery with the formation of an anastomosis between the pseudocyst and part of the gastrointestinal system (stomach, duodenum or Roux loop of jejunum).

Table 6. Mortality in Acute Pancreatitis.⁴⁴⁻⁵⁰

	Median (%)	Range (%)
All cases	5	2-9
Interstitial pancreatitis	3	1-7
Necrotizing pancreatitis	17	8-39
Infected necrosis	30	14-62
Sterile necrosis	12	2-44

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