ACUTE PANCREATITIS

Guidelines for Medical Students
Approved at the meeting of the surgical methodological commission of Danylo Halytsky Lviv National Medical University (Meeting report № ___ on __________ ____, 2019)

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I. Background
The incidence of acute pancreatitis (AP) has increased during the past 20 years. Most patients develop a mild and self-limited course; however, 10% to 20% of patients have a rapidly progressive inflammatory response associated with prolonged length of hospital stay and significant morbidity and mortality. Patients with mild pancreatitis have a mortality rate of less than 1% but, in severe pancreatitis, this increases up to 10% to 30%. The most common cause of death in this group of patients is multiorgan dysfunction syndrome. Mortality in pancreatitis has a bimodal distribution; in the first 2 weeks, also known as the early phase, the multiorgan dysfunction syndrome is the final result of an intense inflammatory cascade triggered initially by pancreatic inflammation. Mortality after 2 weeks, also known as the late period, is often caused by septic complications.

II. Learning Objectives
1. To study the etiological factors of disease, classification of acute pancreatitis, clinical signs, diagnostic methods, treatment and complications ($\alpha = I$).
2. To know the main causes of the disease, typical clinical course and complications, diagnostic value of laboratory and instrumental methods of examination and the principles of the modern conservative and surgical treatment ($\alpha = II$).
3. To be able to collect and analyze the complaints and disease history, thoroughly perform physical examination, determine the order of the most informative examination methods and perform their interpretation, establish clinical diagnosis, justify the indications for surgery, choose adequate method of surgical intervention ($\alpha = III$).
4. To develop creativity in solving complicated clinical tasks in patients with severe or complications of acute pancreatitis ($\alpha = IV$).

III. Purpose of personality development
Development of professional skills of the future specialist, study of ethical and deontological aspects of physicians job, regarding communication with patients and colleagues, development of a sense of responsibility for independent decision making. To know modern methods of treatment of patients with acute pancreatitis and its complications.

IV. Interdisciplinary integration

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<td>Anatomy and histology, blood supply, innervation and function of the pancreas</td>
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<td>Describe macroscopic and microscopic changes of inflamed pancreas</td>
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<td>3. Propedeutics of internal diseases</td>
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<td>4. Pharmacology</td>
<td>Groups and representatives of antibiotics, spasmylytics, analgesics, proton pump inhibitors, antiinflammatory drugs, colloid and crystalloid solutions, drugs for parenteral nutrition</td>
<td>Prescribe conservative treatment for patient with acute pancreatitis</td>
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<td>5. Radiology</td>
<td>Efficiency of radiological investigation in patients with acute pancreatitis</td>
<td>Indications and description of x-ray, ultrasound, computed tomography examination</td>
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**Future subjects**

**Anesthesiology and Critical Care Medicine**

| Clinical signs of urgent conditions that occur in patients with severe and complicated acute pancreatitis, methods of diagnosis and pharmacotherapy | Determine the symptoms of multiorgan dysfunction syndrome, differential diagnosis and treatment |

**Intradisciplinary integration**

| 1. Acute appendicitis                  | Clinical picture of acute appendicitis                                | Check Kocher-Volkovych’s, Blumberg’s, Rovsing’s, psoas, obturator signs |
| 2. Acute cholecystitis                | Clinical picture of acute cholecystitis                              | Check Ortner’s, Kehr’s, Mernphy’s, Mussy’s signs                     |
| 3. Peptic ulcer of stomach and duodenum | Clinical picture of peptic ulcer of stomach and duodenum            | Check Blumberg’s sign, describe plain abdominal film in patient with peptic ulcer perforation |
4. Acute bowel obstruction | Clinical picture of acute bowel obstruction | Describe x-ray signs of acute bowel obstruction
---|---|---
5. Renal colic | Clinical signs of renal colic | Check Pasternasky’s sign

V. Content of the topic and its structuring

ETIOLOGY

The most frequent etiologies of acute pancreatitis are biliary tract disease and alcoholism, which account for about 60-80% of patients. In about 10%, rare etiologies are responsible, but in 10-30% of patients, the etiology remains unknown.

Etiological factors for acute pancreatitis

- **Obstructive**
  - Biliary tract disease (cholelithiasis, choledocholithiasis)
  - Duodenal disorders (annular pancreas, obstructing periampullary polyps, or intraluminal duodenal diverticulae, or obstructing afferent loop after gastrectomy, or obstruction of the duodenum in ventral hernias)
  - Tumors (ampullary or pancreatic)
  - Congenital anomalies (pancreas divisum)
  - Worms (ascariasis, clonorchiasis)
  - Foreign bodies obstructing the papilla
  - Sphincter of Oddi dysfunction

- **Toxic**
  - Alcoholism
  - Scorpion venom
  - Organophosphates
  - Drugs

- **Metabolic**
  - Hypertriglyceridemia (types I, IV, and V)
  - Hypercalcemia (primary or secondary)
  - Uremia

- **Traumatic**
  - Accidental, blunt trauma to the abdomen
  - Iatrogenic, postendoscopic retrograde cholangiopancreatography, postendoscopic sphincterotomy, postoperative

- **Genetic/hereditary**
  - Hereditary pancreatitis

- **Infections**
– Parasitic: ascariasis, clonorchiasis
– Viral: mumps, rubella, hepatitis A, B, C, Coxsackie virus B, echo virus, adenovirus, cytomegaly virus, Epstein-Barr virus, human immunodeficiency virus
– Bacterial: mycoplasma, *Campylobacter jejuni*, leptospirosis, legionella, *Mycobacterium tuberculosis*, *Myobacterium avium complex*

**Vascular**
– Ischemic: hypoperfusion, embolism
– Vasculitis: systemic lupus erythematosus, nodular periarthritis, malignant hypertension

**Idiopathic**

**PATHOPHYSIOLOGY**

The pathophysiology of AP is complex and involves several inflammatory pathways. The initial trigger is the activation within the pancreatic parenchyma of various proteolytic enzymes, usually promoted by the presence of bile and duodenal contents inside pancreatic ducts. In most western countries 30% to 55% of cases are caused by sludge or gallstones, which are known as biliary pancreatitis. The others are a complication from excess nutrition and alcohol intake. The overproduction of inflammatory mediators (cytokines and non-cytokines) may result in the systemic manifestations of AP. Acinar cell damage initiates AP, accounting for local inflammation and local activation of the immune system of the pancreas. Some recent studies have shown that mild AP is associated with extensive apoptotic acinar cell death, whereas acinar cell necrosis with minimal apoptosis is involved in severe AP.

Most researchers believe that AP is the final result of abnormal pancreatic enzyme activation inside acinar cells. Immunolocalization studies have shown that after 15 minutes of pancreatic injury, both zymogen granules and lysosomes colocalize inside the acinar cells. The fact that zymogen and lysosome colocalization occurs before amylase level elevation, pancreatic edema, and other markers of pancreatitis are evident suggests that colocalization is an early step in the pathophysiology and not a consequence of pancreatitis. In addition, the inflammatory response seen in AP can be prevented if acinar cells are pretreated with cathepsin B inhibitors. In vivo studies have also shown that cathepsin B knockout mice have a significant decrease in the severity of pancreatitis.

Pancreatic acinar cells can produce cytokines and chemokines that are involved in the inflammatory response, including the inflammasome-associated factors interleukin-6 (IL-6), IL-18 and caspase-1, which are found in the basolateral region of acinar cells. IL-6, which is known to be involved in the signal transducer and activator of transcription 3/suppressor of cytokine signaling-3 (STAT3/SOCS3) cascade, transmits signals by binding to its membrane-bound receptor, IL-6 receptor, and is ubiquitously expressed. The inflammation associated nuclear factor kappa B induced myeloid cell secreting IL-6, and the effects of IL-6 were mediated by complexation with soluble IL-6 receptor, which is known as trans-signaling. The trans-signaling of IL-6 stimulated phosphorylation of STAT3 and the production of
the neutrophil attractant chemokine ligand 1 in pancreatic acinar cells. The expression of cytokines and chemokines, as well as the inflammasome-associated IL-18 and caspase-1, indicate that the inflammatory mediators released during the early response to lipopolysaccharide are produced exclusively by pancreatic acinar cells. In addition, a recent study suggested that the alcohol-exacerbated lipopolysaccharides response that initiates sub-clinical AP is mediated by acinar cells. Thus, acinar cells are the major source of inflammatory mediators after early pancreatic injury and during the early onset of sub-clinical AP.

Acinar damage by such inflammatory mediators induces the expression of endothelial adhesion molecules and results in a vicious circle that determines an extensive involvement of the vascular endothelium, which in turn generates vasodilation, increased capillary permeability and interstitial edema. In most of these cases the inflammatory process is similar to that of serious sepsis, which leads to multiple organ failure and death. Furthermore, as is the case with sepsis, genetic polymorphisms for some cytokines are associated with prognosis. Meanwhile, free oxygen radicals regulate necrosis extent in acinar cells, the development of pancreatic edema, inflammatory cell sequestration within the pancreas, and the release of inflammation mediators from both acinar and non-acinar cells in the pancreas. The decreased plasma antioxidant levels (total ascorbic acid) and the increased release of lipid peroxidation byproducts are significantly reflected in patients with AP. The body has a number of free oxygen radical-clearing systems, both enzymatic (superoxide dismutase, catalase, myeloperoxidase, and glutathione peroxidase) and non-enzymatic (carotenes, ascorbic acid, tocopherol). Uric acid, albumin and ascorbic acid represent most of the antioxidant capability of human plasma. The other elements present include bilirubin, a-tocopherol, a-carotene, tryptophan, tyrosine and selenium. The antioxidant is dependent upon the conditions extant in a specific microenvironment at a given time, and the type of oxidative situation. The antioxidant defense system represents a complex network with interactions, synergisms, and specific actions on a given oxidant. A number of studies in animal models have analyzed the association between oxidative metabolism and pancreatic inflammation. Studies in laboratory animals suggest that pancreatic oxidative stress occurs in early stages following induction. Treatment with antioxidant agents has been seen to reduce acinar cell damage and edema in several animal models. This suggests that ongoing free oxygen radical formation reduces antioxidant defensive systems in cells. Regarding the role of bradykinin and nitric oxide, there is controversy in that on the one hand they seem to relieve pancreatic dysfunction by strengthening vascularization and its secretory capacity while on the other there is the notion that nitric oxide may enhance oxidative stress.

**Phase I** Premature activation of trypsin in pancreatic acinar cells
activation of destructive pancreatic enzymes

**Phase II** Intrapancreatic inflammation (pancreatitis)
activation of systemic inflammatory mediators

**Phase III** Extrapancreatic inflammation (systemic inflammatory response syndrome; SIRS)
CLINICAL SIGNS

The clinical diagnosis of pancreatitis is one of exclusion. The other upper abdominal conditions that can be confused with acute pancreatitis include perforated peptic ulcer, a gangrenous small bowel obstruction, and acute cholecystitis. Because these conditions often have a fatal outcome without surgery, urgent intervention is indicated in the small number of cases in which doubt persists.

All episodes of acute pancreatitis begin with severe pain, generally following a substantial meal. Pain is the cardinal symptom. It has been described as „knifing” or „boring through” to the back, and may be relieved by the patient leaning forward. The pain is frequently severe, constant and refractory to the usual doses of analgesics. Pain is usually experienced first in the epigastrium but may be localised to either upper quadrant or felt diffusely throughout the abdomen. There is radiation to the back in about 50 per cent of patients, and some patients may gain relief by sitting or leaning forwards. The suddenness of onset may simulate a perforated peptic ulcer, while biliary colic or acute cholecystitis can be mimicked if the pain is maximal in the right upper quadrant. Radiation to the chest can simulate myocardial infarction, pneumonia or pleuritic pain.

Positioning can be important, because the discomfort frequently improves with the patient in the supine position.

Nausea, repeated vomiting and retching are usually marked accompaniments. The retching may persist despite the stomach being kept empty by nasogastric aspiration. Diarrhea can also occur. Hiccoughs can be troublesome and may be due to gastric distension or irritation of the diaphragm. Vomiting does not relieve the pain, which is more intense in necrotizing than in edematous pancreatitis.

On examination, the appearance may be that of a patient who is well or, at the other extreme, one who is gravely ill with profound shock, toxicity and confusion. Tachypnoea is common, tachycardia is usual, and hypotension may be present. The body temperature is often normal or even subnormal, but frequently rises as inflammation develops. Mild icterus can be caused by biliary obstruction in gallstone pancreatitis, and an acute swinging pyrexia suggests cholangitis. Bleeding into the fascial planes can produce bluish discolouration of the flanks (Grey Turner’s sign) or umbilicus (Cullen’s sign). Neither sign is pathognomonic of acute pancreatitis; Cullen’s sign was first described in association with rupture of an ectopic pregnancy. Subcutaneous fat necrosis may produce small, red, tender nodules on the skin of the legs.

Abdominal examination may reveal distension due to ileus or, more rarely, ascites with shifting dullness. A mass can develop in the epigastrium due to inflammation. There is usually muscle guarding in the upper abdomen, although marked rigidity is unusual. A pleural effusion is present in 10-20 per cent of patients. Pulmonary oedema and pneumonitis are also described and may give rise to the
differential diagnosis of pneumonia or myocardial infarction. The patient may be confused and exhibit the signs of metabolic derangement together with hypoxaemia.

In severe cases, hemodynamic instability is evident (10%) and hematemesis or melena sometimes develops (5%); in addition, patients with severe acute pancreatitis are often pale, diaphoretic, and listless.

Occasionally, in the extremities, muscular spasm may be noted secondary to hypocalcemia.

Rarely, abnormalities on funduscopic 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.

LABORATORY TESTS

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 3 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. Preferably, the amylase P level should be measured, which is somewhat more specific to pancreatic pathology. Elevations can occur in patients with small intestinal obstruction, mesenteric ischemia, tubo-ovarian disease, renal insufficiency, or macroamylasemia. Rarely, elevations may reflect parotitis. The serum half-life of amylase is short, and elevations generally return to the reference ranges within a few days.

Lipase has a slightly longer half-life and its 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 elevated amylase levels. Lipase levels remain high for 12 days. In patients with chronic pancreatitis (usually caused by alcohol abuse), lipase levels may be elevated in the presence of a normal serum amylase level.

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 the prognosis.

Determine alkaline phosphatase, total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels to search for evidence of gallstone pancreatitis. An ALT level higher than 150 U/L suggests gallstone pancreatitis and a more fulminant disease course.

Obtain measurements for blood urea nitrogen (BUN), creatinine, and electrolytes; a great disturbance in the electrolyte balance is usually found, secondary to third spacing of fluids. Measure blood glucose level because it may be elevated from B-cell injury in the pancreas.

Measure calcium, cholesterol, and triglyceride levels to search for an etiology of pancreatitis (eg, hypercalcemia or hyperlipidemia) or complications of pancreatitis (eg, hypocalcemia resulting from saponification of fats in the retroperitoneum).
However, be aware that baseline serum triglyceride levels can be falsely lowered during an episode of acute pancreatitis.

A complete blood count (CBC) demonstrates leukocytosis (white blood cell [WBC] count higher than 12,000/µL) with the differential being shifted toward the segmented polymorphonuclear (PMN) cells. Leukocytosis may represent inflammation or infection.

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.

A C-reactive protein (CRP) value can be obtained 24-48 hours after presentation to provide some indication of prognosis. Higher levels have been shown to correlate with a propensity toward organ failure. A CRP value in double figures (ie, ≥ 10 mg/dL) strongly indicates severe pancreatitis. CRP is an acute-phase reactant that is not specific for pancreatitis.

If a patient is dyspneic. Whether tachypnea is due to acute respiratory distress syndrome (ARDS) or diaphragmatic irritation must be determined.

Lactic dehydrogenase (LDH), BUN, and bicarbonate levels should be measured both at admission and at 48 hours in order to help determine the Ranson criteria for survival.

Immunoglobulin G4 (IgG4) levels can be checked to evaluate for autoimmune pancreatitis. However, this test is not specific, because IgG4 levels can be elevated in as many as 10% of patients with acute pancreatitis who do not have autoimmune pancreatitis.

Trypsin and its precursor trypsinogen-2 in both the urine and the peritoneal fluid have been evaluated as possible markers for acute pancreatitis (especially post-ERCP 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 chemotactic 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.

**IMAGING STUDIES**

Plain radiology is of value at the time of admission. A chest X-ray can exclude free intraperitoneal gas as a result of visceral perforation as alternative diagnosis, and may demonstrate pulmonary complications of AP (pleural effusions and acute respiratory distress syndrome). Plain abdominal X-ray helps exclude other causes of abdominal pain (e.g. obstruction), but in AP it is usually either normal, or demonstrates ileus. Plain radiology is of limited value following admission and has been replaced by axial imaging in the context of clinical deterioration, or for disease follow-up.
Findings on plain radiographs associated with acute pancreatitis are nonspecific and include ileus that may be generalized or localized to a segment of small intestine ("sentinel loop") or transverse colon ("colon cut-off sign"), psoas muscle margins that are obscured by retroperitoneal edema, an elevated hemidiaphragm, pleural effusions, and basilar atelectasis.

All patients with acute pancreatitis should have an ultrasonic assessment of the biliary tree within 24 h of admission. In those with gallstones, the majority will have mild disease, and this will facilitate definitive treatment of cholelithiasis prior to discharge. In the emergency situation, ultrasonography can be difficult due to a number of factors, including the presence of intraluminal bowel gas or lack of patient cooperation. Therefore, in patients with a negative initial US, and no other obvious aetiological factor, the US should be repeated prior to discharge before excluding gallstones as a potential aetiological factor.

CT helps to confirm the diagnosis when doubt exists, but it is not required in every patient with AP. The role and timing of CT are determined by clinical condition and can be divided into:

– On admission to exclude other acute pathology, e.g. mesenteric ischemia.
– Early to differentiate interstitial from necrotizing AP if condition deteriorates.
– Late to detect local complications of AP, e.g. fluid collections and necrosis.
– Follow-up to monitor local complications and assess response to therapy.

Non-contrast CT scanning may also be of value in the setting of renal failure by identifying fluid collections and/or extraluminal air.

Contrast-enhanced computed tomography (CT) is currently the best modality to evaluate the pancreas, especially if the study is performed using a multidetector CT scanner. The most valuable contrast phase to evaluate the pancreatic parenchyma is the portal venous phase (65 to 70 seconds after contrast injection), which allows evaluation of the viability of the pancreatic parenchyma amount of peripancreatic inflammation and presence of intra-abdominal free air or fluid collections.

The CT severity index of Balthazar may be used to radiologically grade the severity of AP and may be used to compare treatment outcomes in different patient groups, but is of limited value in guiding individual patient management.

*Balthazar CT severity index*
Magnetic resonance imaging (MRI) offers a realistic alternative to contrast-enhanced CT in the assessment of patients with acute pancreatitis. The avoidance of cumulative radiation exposure, potentially nephrotoxic iodinated contrast media, and the excellent contrast sensitivity and spatial resolution would make it an attractive alternative. Axial T1- and T2-weighted scans produce images analogous to those of CT. Gadolinium contrast enhancement can infer viability and improve anatomical definition. Heavily T2-weighted image acquisition, using a single breath hold and long repetition (TR) and echo (TE) times, results in little signal being produced by solid tissue, and a high signal from static fluid in the biliary and pancreatic ducts, enabling images anatomically comparable to those of ERCP to be produced.

Whilst technically feasible in most centers, the MR environment is unsuitable for patients requiring significant circulatory or respiratory support, and at present few centers have the capability to perform MR-guided intervention. Contrast-enhanced CT therefore remains the imaging modality of choice for assessment and intervention in severe acute pancreatitis. However, MR has a role in the follow-up of acute inflammatory collections, where it is superior to CT in determining the extent of solid material within a collection, and in excluding choledocholithiasis in selected patients.
Abdominal magnetic resonance imaging (MRI) is also useful to evaluate the extent of necrosis, inflammation, and presence of free fluid. However, its cost and availability, and the fact that patients requiring imaging are critically ill and need to be in intensive care units, limit its applicability in the acute phase. Although magnetic resonance cholangiopancreatography (MRCP) is not indicated in the acute setting of AP, it has an important role in the evaluation of patients with unexplained or recurrent pancreatitis because it allows complete visualization of the biliary and pancreatic duct anatomy. In addition, IV administration of secretin increases pancreatic duct secretion, which causes a transient distention of the pancreatic duct. For example, secretin MRCP is useful in patients with AP and no evidence of a predisposing condition to rule out pancreas divisum, intraductal papillary mucinous neoplasm (IPMN), or the presence of a small tumor in the pancreatic duct.

In the setting of gallstone pancreatitis, endoscopic ultrasound (EUS) may play an important role in the evaluation of persistent choledocholithiasis. Several studies have shown that routine ERCP for suspected gallstone pancreatitis reveals no evidence of persistent obstruction in most cases and may actually worsen symptoms because of manipulation of the gland. EUS has been proven to be sensitive for identifying choledocholithiasis; it allows for examination of the biliary tree and pancreas with no risk of worsening the pancreatitis. In patients in whom persistent choledocholithiasis is confirmed by EUS, ERCP can be used selectively as a therapeutic measure.

Endoscopic retrograde cholangiopancreatography (ERCP) has no role in diagnosing AP. Therapeutic application of ERCP in moderate to severe acute gallstone pancreatitis has been shown by several controlled clinical trials to lower morbidity and mortality when compared to traditional medical treatment alone. ERCP is also utilized in the differential diagnosis and elective treatment of recurrent unexplained pancreatitis secondary to sphincter Oddi dysfunction, pancreatic divisum, and microlithiasis.

**DIAGNOSTIC CRITERIA FOR ACUTE PANCREATITIS**

A diagnosis of AP requires two of the following three criteria:

1. Characteristic abdominal pain.
2. Serum amylase or lipase $\geq 3$ times upper limit of normal.
3. Computed tomography (CT) findings consistent with AP.

**Differential diagnosis**

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<th>Differentiating tests</th>
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<tr>
<td>Peptic ulcer disease</td>
<td>Longstanding epigastric pain, which does not generally radiate to the back; reflux; heartburn; and anorexia. Identifiable causes such as non-steroidal anti-</td>
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<td>May improve with proton pump inhibitors, lifestyle modifications, and H pylori treatment. Normal lipase and amylase. Tonometry may show</td>
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<tr>
<td>Condition</td>
<td>Description</td>
<td>Diagnosis</td>
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<td>Perforated viscus</td>
<td>Will present with acute abdomen, peritoneal signs, tachycardia, and sepsis. Generally the abdomen is rigid and tender in all 4 quadrants, with guarding.</td>
<td>Normal lipase. May have elevated amylase (usually less marked than that seen in acute pancreatitis). Plain x-rays show sub-diaphragmatic air.</td>
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<td>Oesophageal spasm</td>
<td>Dysphagia, odynophagia, weight loss, history of retrosternal pain. Physical examination may be normal.</td>
<td>A swallow study may demonstrate a contracted and abnormal-appearing oesophagus with increased pressures on oesophageal manometry.</td>
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<td>Intestinal obstruction</td>
<td>History of abdominal surgeries (especially colon resection, caesarean sections, and aortic procedures). Hernias in the physical examination. Presents with abdominal distension (depends on the level of obstruction), tympanism, decreased bowel sounds, anorexia, emesis (quality depends on location of obstruction), obstipation, or constipation.</td>
<td>Normal lipase and amylase. Acute abdominal series will show ground glass appearance, air-fluid levels, distended bowel loops, absence of distal gas, pneumatiso. An abdomen/pelvic CT scan may be more diagnostic, and will show point of transition and potentially identify aetiology (such as volvulus, hernias, intussusception, masses).</td>
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<td>Abdominal aorta aneurysm</td>
<td>Cardiovascular risk factors: hyperlipidaemia, tobacco, diabetes mellitus, homocystinaemia. Acute tearing-like abdominal pain, pulsating abdominal mass, hypotension, and mottled lower extremities.</td>
<td>High index of suspicion is necessary to make a rapid diagnosis and improve outcomes. In stable patients, where history and physical examination are equivocal, a CT angiography may be useful as a rapid way to</td>
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<tr>
<td>Condition</td>
<td>Description</td>
<td>Diagnosis and Evaluation</td>
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<tr>
<td>Cholangitis</td>
<td>with decreased pulses and abdominal distension. Several clinical findings are present more frequently in cholangitis, such as fever (95%), right upper quadrant pain (90%), and jaundice (80%).</td>
<td>If too unstable for radiographic evaluation, patients usually go directly to surgery. Normal lipase and amylase. Blood cultures are usually positive, especially during episodes of chills, with Escherichia coli and Klebsiella as the most common micro-organisms isolated from infected bile.</td>
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<td>Choledocholithiasis</td>
<td>Charcot’s triad (jaundice, right upper quadrant pain, and fever) present in 70% of patients, altered mental status, and hypotension indicate biliary sepsis, usually caused by gram-negative bacteria. Patient may have a history of gallstones, peri-ampullary neoplasms, or biliary manipulation such as endoscopic retrograde cholangiopancreatography (ERCP).</td>
<td>Several clinical findings are present more frequently in cholangitis, such as fever (95%), right upper quadrant pain (90%), and jaundice (80%). Normal lipase and amylase. Ultrasound will show gallstones, stones within the common bile duct with extra-hepatic and/or intra-hepatic duct dilatation. Chemistry will show biochemical obstruction, with increased levels of total and direct bilirubin, alkaline phosphatase, gamma-GT, and a slight increase in ALT/AST but normal levels of pancreatic enzymes (especially lipase).</td>
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<td>Cholecystitis</td>
<td>Pain is generally triggered after a fatty meal and localised in the right upper quadrant. More common in overweight females between 40 and 50 years of age. Anorexia, nausea, and vomiting may be present. May show a positive</td>
<td>Normal lipase and amylase. A right upper quadrant ultrasound will show thickened gallbladder wall, stones with acoustic shadows, biliary sludge, peri-cholecystic fluid, and sonographic Murphy’s sign, and allows evaluation of the</td>
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<tr>
<td>Condition</td>
<td>Symptoms</td>
<td>Tests/Imaging</td>
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<td>Murphy's sign and low-grade fever.</td>
<td>duc system. Can suggest pancreatic head inflammation. May show mild leukocytosis and a very mild elevation of liver enzymes. A hepatobiliary iminodiacetic acid (HIDA) scan is diagnostic when there is no filling of the gallbladder or with delayed emptying of the radiotracer.</td>
<td>Murphy's sign, leukocytosis, liver enzymes, HIDA scan.</td>
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<td>Viral gastroenteritis</td>
<td>Generalised non-specific abdominal pain, anorexia, nausea, emesis, diarrhoea, and dehydration. Is usually a self-limiting viral infection but if fever is documented, bacterial and invasive organisms should be suspected. Consider in travellers and immunosuppressed patients. Consider osmotic and secretory diarrhoea from hx.</td>
<td>Normal lipase and amylase. Important to obtain serum electrolytes and an FBC. Hypokalaemia and alkalosis may be seen secondary to diarrhoea, vomiting, and dehydration. Stool examination for microscopy, culture, osmolality, ova, parasites, Clostridium difficile toxin, and white blood cells may help in identifying the causative factor.</td>
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<td>Hepatitis</td>
<td>Jaundice, right upper quadrant pain, anorexia, and general malaise. Choluria and acholia may be seen. Examination: tenderness to palpation over the right upper quadrant and enlarged liver.</td>
<td>Normal lipase and amylase. Elevated liver function tests are characteristic. AST/ALT in the range of the 1000 units/L is not rare. Serological titres can make diagnosis of aetiological cause. Radiographic studies not important for its diagnosis.</td>
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<tr>
<td>Mesenteric ischaemia</td>
<td>Patients are usually older, may have a history of atrial fibrillation and risk factors for peripheral vascular disease. Hypercoagulable states may lead to bowel necrosis. Pain is usually out of proportion to</td>
<td>High index of suspicion of diagnosis is necessary. Angiography and CT scan may be useful in diagnosis as well as lactic acid levels. Normal lipase. May have elevated amylase (usually less marked than that seen</td>
</tr>
</tbody>
</table>
Myocardial infarction

Pain is usually retrosternal with radiation to jaw, neck, and left upper extremity. Associated with shortness of breath, nausea, vomiting, and diaphoresis. Cardiovascular risk factors in the history.

Elevated cardiac enzymes (creatine kinase or creatine phosphokinase, troponins), ECG changes, and clinical scenario make the diagnosis.
Normal lipase and amylase. Cardiac catheterisation, perfusion scans, and echocardiograms are useful during the work-up of cardiac ischaemia.

**ASSESSMENT OF SEVERITY OF DISEASE**

Several single parameters and more or less complex scoring systems for the prediction of the severity of AP have been developed and clinically evaluated and all of them have been shown to be associated with advantages and disadvantages. The HAPS score (harmless acute pancreatitis score) was developed to identify patients with mild AP who can be treated as outpatients. Patients without rebound tenderness and/or guarding, a normal hematocrit, and a normal serum creatinine concentration have a high probability (positive predictive value: 98%-98.7%) to have a harmless course of the disease.

One of the oldest and probably best known and heavily used scores to predict a severe course of pancreatitis was developed in the early 70ties by John Ranson and colleagues. The Ranson score is based on the presence or absence of simple parameters and is assessed differently at the time of admission (5 parameters; possible scores: 0-5) and 48 h later (6 parameters; possible scores: 0-6). Although a score ≥ 3 has a high sensitivity and specificity regarding a severe course of pancreatitis (83.9% and 78.0%, respectively) and a negative predictive value of 94.5%, the severity can be predicted no earlier than 48 h after admission. A modification of the Ranson score by Clemens Imrie and colleagues (Imrie score or Glasgow score) was first reported in 1978 and is still widely used and has a similar accuracy as the Ranson score.

Currently, the score with the highest sensitivity regarding prediction of a severe course is the Acute Physiology And Chronic Health Evaluation (APACHE) II score. Originally developed to predict mortality in intensive care patients, a value ≥ 8 of the APACHE II score predicts a severe course of AP with a sensitivity of 65%-83%, specificity of 77%-91%, positive predictive value (PPV) of 23%-69%, and negative predictive value (NPV) of 86%-99%. However, the determination of an APACHE II score in a clinical patient is complex and time-consuming as it utilizes more than 15 parameters, which limits the clinical value of this score.
A score that was developed and validated more recently in almost 18000 patients, is the BISAP (Bedside Index of Severity in Acute Pancreatitis) score. The main advantage of the BISAP score is its simplicity. One point each is given for blood urea nitrogen (BUN) > 8.9 mmol/L, impaired mental status (Glasgow Coma Scale < 15), presence of SIRS, age > 60 years, and pleural effusion. A score ≥ 3 is predictive for a severe course (observed mortality of > 5%) with a sensitivity of 83% and a PPV of 76.9%. One disadvantage of the BISAP score is, that this score cannot easily distinguish patients with transient and persistent organ failure and therefore may overestimate severity and preclude differentiation between moderate and severe AP.

In addition to the laboratory/clinical scoring systems described above there are scoring systems based on imaging results to assess and predict the severity of AP. A CT scan for diagnostic purposes and severity assessment has been-and probably still is standard practice in many centers. The Balthazar score, developed in 1985, categorizes patients with AP into 5 groups (A-E) according to pancreatic and peripancreatic changes diagnosed by CT. In 1990, Balthazar et al. modified this score, including assessment of the extent of pancreatic necrosis and named this score Computed Tomography Severity Index (CTSI). The CTSI is probably the most frequently used imaging score to assess severity in patients with AP and a score ≥ 4 has a negative predictive value of 94%-97% and a positive predictive value 53%-69% regarding the clinical severity of disease. In addition to the Balthazar score and the CTSI, several other scores, e.g., pancreatic size index (PSI), mesenteric edema and peritoneal fluid (MOP) score, extrapancreatic (EP) score, extrapancreatic inflammation on CT (EPIC) score, modified CTSI (MCTSI), and MR severity index (MRSI) have been developed and evaluated. However, none of these imaging scores were shown to be superior to clinical scoring systems. Thus, a CT on admission to predict severity of AP cannot be recommended at the current time.

In addition to laboratory/clinical and imaging scoring systems, single parameters have been evaluated to assess and predict severity.

A lot of research has been done evaluating hematocrit as an indicator for hemoconcentration. The first prospective cohort study showed a high NPV for a hematocrit ≥ 44 % (93% on admission and 97% 24 h later) but a poor PPV (26% and 27%, respectively) regarding organ failure in AP. Similar results were obtained by several other studies focusing on the usefulness of hematocrit to predict a severe course of AP, organ failure, pancreatic necrosis, or death. Due to its high negative predictive value, its low cost, and the ease of measurement, the hematocrit has value in predicting a non-severe course of AP.

The disruption of water balance can lead to hypoperfusion and a disturbance of pancreatic microcirculation, which in turn correlates with the severity of AP. Understanding the water balance and the resulting changes in laboratory tests can help to predict severity and outcome of AP. In addition to hematocrit, other parameters, that mirror intravascular volume depletion, can also be helpful.

Serum creatinine has been identified as a predictor for pancreatic necrosis. Also, more recently, an estimated glomerular filtration rate (GFR) < 90 mL/min per 1.73
m² on admission has been shown to predict pancreatic necrosis with a sensitivity, specificity, PPV, and NPV of 78.1%, 71%, 64%, and 83%, respectively. While only one study has described GFR as a predictor of severity, BUN has been evaluated for many years and has been shown to be a good predictor for severity in AP in several large studies. A rise in BUN > 1.8 mmol/L after 48 h had already been included in the Ranson score 40 some years ago, is one of the 4 parameters used in the BISAP score, and has also been shown to have a high predictive value as a single parameter.

Besides parameters focusing on water balance and microcirculation, laboratory parameters suggesting the presence of an inflammatory process have been used as a predictor of severity. The most intensively studied parameter is CRP. In one study, a serum CRP concentration of 150 mg/L or greater predicted severe AP at 36 h after admission with a sensitivity, specificity, PPV, and NPV of 86%, 87%, 75%, and 93%, respectively. However, the prediction of severity was only possible more than 24 h after admission, which, on average, is about 50 h after the onset of pain. Also, several other studies showed a high predictive value of CRP during the course of AP in regards to severity, but a very low predictive value on admission.

Procalcitonin appears to be a valuable tool to discriminate between sterile and infected necrosis within the first days of AP. However, data on the ability to predict the course of AP are not consistent.

A blood glucose concentration < 6.9 mmol/L on admission has a high negative predictive value (92%) for pancreatic necrosis and also can serve as a predictor for severity. Blood glucose is easy, fast, and inexpensive to determine and widely available and therefore should be included in the risk stratification.

**Ranson criteria (non-gallstone pancreatitis)**

Used for prediction of severe acute pancreatitis - not diagnosis.

**Criteria on admission:**
- age >55 years;
- glucose > 11.1 mmols/L (200 mg/dL);
- WBC count > 16 x 10^9/L (16 x 10^3/microlitre);
- serum AST (SGOT) > 250 units/L;
- serum LDH > 350 units/L.

**Criteria after 48 hours** of admission:
- Hct fall > 10%;
- estimated fluid sequestration > 6 L;
- base deficit > 4 mEq/L;
- blood urea nitrogen rise > 1.8 mmols/L (5 mg/dL);
- serum calcium < 2 mmols/L (8 mg/dL);
- PO2 < 8 kPa (60 mmHg).

Number of criteria and approximate mortality (%):
- 0 to 2 = 0%
• 3 to 4 = 15%
• 5 to 6 = 50%
• >6 = 100%.

**Ranson criteria (gallstone-associated)**
Used for prediction of severe acute pancreatitis - not diagnosis.
Criteria **on admission:**
• age >70 years;
• glucose >12.2 mmols/L (220 mg/dL);
• WBC count >18 x 10^9/L (18 x 10^3/ microlitre);
• serum AST (SGOT) >250 units/L;
• serum LDH >400 units/L.
Criteria **after 48 hours** of admission:
• Hct fall >10%;
• estimated fluid sequestration >4 L;
• base deficit >5 mEq/L;
• blood urea nitrogen rise >0.7 mmols/L (2 mg/dL);
• serum calcium <2 mmols/L (8 mg/dL).

**Glasgow prognostic criteria (Imrie’s criteria)**

The Glasgow system is a simple prognostic system that uses age, and 7 laboratory values collected during the first 48 hours following admission for pancreatitis, to predict severe pancreatitis. It is applicable to both biliary and alcoholic pancreatitis.

A point is assigned if a certain breakpoint is met at any time during that 48-hour period.

The parameters and breakpoints are:

• Age >55 years = 1 point
• Serum albumin <32 g/L (3.2 g/dL) = 1 point
• Arterial PO2 on room air <8 kPa (60 mmHg) = 1 point
• Serum calcium <2 mmols/L (8 mg/dL) = 1 point
• Blood glucose >10.0 mmols/L (180 mg/dL) = 1 point
• Serum LDH >600 units/L = 1 point
• Serum urea nitrogen >16.1 mmols/L (45 mg/dL) = 1 point
• WBC count >15 x 10^9/L (15 x 10^3/microlitre) = 1 point.

The addition of the parameter points yields the Glasgow prognostic criteria. The score can range from 0 to 8. If the score is >2, the likelihood of severe pancreatitis is high. If the score is <3, severe pancreatitis is unlikely.
Bedside index of severity in acute pancreatitis score and observed mortality by bedside index of severity in acute pancreatitis score

The extrapancreatic inflammation on computed tomography score

The extrapancreatic inflammation on computed tomography (EPIC) score assesses the severity of acute pancreatitis based on extrapancreatic complications. The score ranges from 0 to 7 based on CT findings. Scores 0 to 3 are associated with 0% mortality; scores 4 to 7 are associated with 67% mortality.

Signs of extrapancreatic inflammation and score:

- Pleural effusion
  - None = 0
  - Unilateral = 1
  - Bilateral = 2.
- Ascites in any of these locations: perisplenic, periphepatic, interloop, pelvis
  - None = 0
  - One location = 1
  - More than one location = 2.
- Retroperitoneal inflammation
  - None = 0
  - Unilateral = 1
  - Bilateral = 2.
- Mesentric inflammation
CLASSIFICATION

The Atlanta Classification

In the majority of cases, acute pancreatitis is a self-limiting disease and complete functional restitution of the gland is the rule. Nevertheless, 10–15% of the patients develop severe courses characterized by life-threatening complications such as multiple organ failure and/or severe sepsis. These cases are associated with mortality rates of 15–25%, even if the patients are transferred to specialized centers with expertise in the treatment of this disease.

The Atlanta classification (1992) has introduced the term „severe acute pancreatitis” in differentiation to „mild acute pancreatitis”. Patients suffering from SAP bear a high risk of developing life-threatening complications and complicated courses of the disease. SAP is today defined by occurrence of one or more systemic (organ failure) or local complication during the course of the disease.

The Atlanta classification defines six systemic complications that characterize the severe form of acute pancreatitis:
1. Pulmonary insufficiency (arterial oxygen tension of 60 mmHg or less).
2. Renal insufficiency (serum creatinine >2.0 mg/dl after rehydration).
3. Shock (systolic blood pressure of 90 mmHg or less over at least 15 min).
4. Gastrointestinal bleeding (>500 ml/24 h).
5. Coagulopathy (platelets 100,000/mm3 or less, fibrinogen less than 1.0 g/l and fibrin split products more than 80 μg/ml)
6. Metabolic disturbances (serum calcium <7.5 mg/dl)

In addition, two of the most widely used scoring systems were accepted for discrimination between mild acute pancreatitis and SAP: the Ranson criteria (three or more criteria) and the Acute Physiology And Chronic Health Evaluation (APACHE) II score (eight or more points)

From the pathomorphological point of view, four entities were defined that characterize SAP:
1. Pancreatic necrosis, defined by diffuse or focal area(s) of nonviable pancreatic parenchyma, typically associated with peripancreatic fat necrosis.
2. Acute fluid collections, defined as peripancreatic collections of fluid, located in or near the pancreas, lacking a wall of surrounding granulation or fibrous tissue.
3. Acute pseudocyst, defined as a collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue.
4. Pancreatic abscess, defined as a circumscribed intra-abdominal collection of pus, usually in proximity to the pancreas, containing little or no pancreatic necrosis.

Classification of acute pancreatitis-2012 (revision of the Atlanta classification) identifies 2 phases of acute pancreatitis – early (first 1 or 2 weeks) and late (thereafter). Acute pancreatitis can be either edematous interstitial pancreatitis or necrotizing pancreatitis, the latter involving necrosis of the pancreatic parenchyma and peripancreatic tissues (most common), pancreatic parenchyma alone (least common), or just the peripancreatic tissues (~20%).

Severity of the disease is categorized into 3 levels: mild, moderately severe, and severe. Mild acute pancreatitis lacks both organ failure (as classified by the modified Marshal scoring system) and local or systemic complications. Moderately severe acute pancreatitis has transient organ failure (organ failure of <2 days), local complications, and/or exacerbation of coexistent disease. Severe acute pancreatitis is defined by the presence of persistent organ failure (organ failure that persists for ≥2 days).

Local complications are defined by objective criteria based primarily on contrast-enhanced computed tomography; these local complications are classified as acute peripancreatic fluid collections, pseudocyst (which are very rare in acute pancreatitis), acute (pancreatic/peripancreatic) necrotic collection, and walled-off necrosis.
**Modified Marshall scoring system for organ dysfunction**

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Score 0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (PaO₂/FiO₂)</td>
<td>&gt;400</td>
<td>301–400</td>
<td>201–300</td>
<td>101–200</td>
<td>≤101</td>
</tr>
<tr>
<td>Renal†</td>
<td>≤134</td>
<td>134–169</td>
<td>170–310</td>
<td>311–439</td>
<td>&gt;439</td>
</tr>
<tr>
<td>(serum creatinine, μmol/l)</td>
<td>&lt;1.4</td>
<td>1.4–1.8</td>
<td>1.9–3.6</td>
<td>3.6–4.9</td>
<td>&gt;4.9</td>
</tr>
<tr>
<td>(serum creatinine, mg/dl)</td>
<td>&gt;90</td>
<td>&lt;90, fluid responsive</td>
<td>&lt;90, not fluid responsive</td>
<td>&lt;90, pH&lt;7.3</td>
<td>&lt;90, pH&lt;7.2</td>
</tr>
<tr>
<td>Cardiovascular (systolic blood pressure, mm Hg)†</td>
<td>&gt;90</td>
<td>&lt;90, fluid responsive</td>
<td>&lt;90, not fluid responsive</td>
<td>&lt;90, pH&lt;7.3</td>
<td>&lt;90, pH&lt;7.2</td>
</tr>
</tbody>
</table>

For non-ventilated patients, the FiO₂ can be estimated from below:

<table>
<thead>
<tr>
<th>Supplemental oxygen (l/min)</th>
<th>FiO₂ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room air</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>6–8</td>
<td>40</td>
</tr>
<tr>
<td>9–10</td>
<td>50</td>
</tr>
</tbody>
</table>

* A score of 2 or more in any system defines the presence of organ failure.
† A score for patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine >134 μmol/l or >1.4 mg/dl.

**Definitions of morphological features of acute pancreatitis**

**Interstitial oedematous pancreatitis** Acute inflammation of the pancreatic parenchyma and peripancreatic tissues, but without recognisable tissue necrosis **CECT criteria**

- Pancreatic parenchyma enhancement by intravenous contrast agent
- No findings of peripancreatic necrosis (see below)

**Necrotising pancreatitis** Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis **CECT criteria**

- Lack of pancreatic parenchymal enhancement by intravenous contrast agent and/or
- Presence of findings of peripancreatic necrosis (see below—ANC and WON)

**APFC (acute peripancreatic fluid collection)** Peripancreatic fluid associated with interstitial oedematous pancreatitis with no associated peripancreatic necrosis. This term applies only to areas of peripancreatic fluid seen within the first 4 weeks after onset of interstitial oedematous pancreatitis and without the features of a pseudocyst. **CECT criteria**

- Occurs in the setting of interstitial oedematous pancreatitis
- Homogeneous collection with fluid density
- Confined by normal peripancreatic fascial planes
- No definable wall encapsulating the collection
- Adjacent to pancreas (no intrapancreatic extension)

**Pancreatic pseudocyst** An encapsulated collection of fluid with a well defined inflammatory wall usually outside the pancreas with minimal or no necrosis. This entity usually occurs more than 4 weeks after onset of interstitial oedematous pancreatitis to mature. **CECT criteria**

- Well circumscribed, usually round or oval
- Homogeneous fluid density
- No non-liquid component
- Well defined wall; that is, completely encapsulated
- Maturation usually requires >4 weeks after onset of acute pancreatitis; occurs after interstitial oedematous pancreatitis
ANC (acute necrotic collection) A collection containing variable amounts of both fluid and necrosis associated with necrotising pancreatitis; the necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues. CECT criteria

- Occurs only in the setting of acute necrotising pancreatitis
- Heterogeneous and non-liquid density of varying degrees in different locations (some appear homogeneous early in their course)
- No definable wall encapsulating the collection
- Location—intrapancreatic and/or extrapancreatic

WON (walled-off necrosis) A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well defined inflammatory wall. WON usually occurs >4 weeks after onset of necrotising pancreatitis. CECT criteria

- Heterogeneous with liquid and non-liquid density with varying degrees of loculations (some may appear homogeneous)
- Well defined wall, that is, completely encapsulated
- Location—intrapancreatic and/or extrapancreatic
- Maturation usually requires 4 weeks after onset of acute necrotising pancreatitis

The latest classification of AP (Determinant-based classification of acute pancreatitis severity): (1) mild AP (MAP) is characterized by the absence of both pancreatic (peri) necrosis and organ failure; (2) moderate AP is characterized by the presence of sterile (peri)pancreatic necrosis and/or transient organ failure; (3) severe AP (SAP) is characterized by the presence of either infected (peri)pancreatic necrosis or persistent organ failure; and (4) critical AP is characterized by the presence of infected (peri) pancreatic necrosis and persistent organ failure.

Organ failure is defined for 3 organ systems (respiratory, cardiovascular and renal) based on the worst measurement over a 24-h period. In patients without preexisting organ dysfunction, organ failure is defined as either a score of 2 or more in the assessed organ system using the Sepsis-related Organ Failure Assessment (SOFA) score or when the relevant threshold is breached, as shown: (1) respiratory: partial pressure of oxygen (PaO\textsubscript{2}) < basal 60 mmHg (with supplementary O\textsubscript{2}); or PaO\textsubscript{2}/fraction of inspiration O\textsubscript{2} (FiO\textsubscript{2}) ≤ 300 mmHg (≤ 40 kPa); (2) cardiovascular: systolic arterial pressure (SAP) less than 90 mmHg or a reduction of 40 mmHg in basal SAP, with signs of tissue hypoperfusion (lactate > 3 mmol/L); Saturation of central venous oxygen SvcO\textsubscript{2} < 70%; and (3) renal: an increase of basal creatinine by 2 (AKI-2, RIFLE-I) and/or reduction of urinary flow (oliguria) < 0.5 mL/kg per hour × 12 h.

The most accurate marker in defining the severity of disease is dysfunction/persistent organ failure (lasting over 48 h). The scoring system was chosen for its simplicity, universal applicability in clinical practice and in research and its ability to stratify disease. Some others like the SOFA scoring system and APACHE II for patients managed in a critical care unit, which includes inotropic and respiratory support, can be used to assess the severity of dysfunction/organ failure. However, for an easier hierarchy, these scores are not included in current
classifications. A score equal to or greater than 2 in each system defines the presence of organ failure.

The presence or absence of local complications is very important. Local complications of AP are: acute peri-pancreatic fluid collections, acute necrotic collections, pancreatic pseudocyst and walled off necrosis. Other local complications of AP include perturbation of gastric emptying, splenic or portal vein thrombosis, and necrosis of the colon.

**Sequential Organ Failure Assessment score (SOFA score)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration (PaO₂/FiO₂ [mmHg])</td>
<td>&gt; 400</td>
<td>≤ 400</td>
<td>&lt; 300</td>
<td>≤ 200 with respiratory support</td>
<td>≤ 100 with respiratory support</td>
</tr>
<tr>
<td>Coagulation</td>
<td>&gt; 150</td>
<td>≤ 150</td>
<td>&lt; 100</td>
<td>≤ 50</td>
<td>≤ 20</td>
</tr>
<tr>
<td>Liver</td>
<td>0-1.2</td>
<td>1.3-1.9</td>
<td>2-5</td>
<td>6-11.9</td>
<td>&gt; 12</td>
</tr>
<tr>
<td>Cardiovascular Hypotension</td>
<td>No hypotension</td>
<td>MAP &lt; 70 mmHg</td>
<td>Dopamine ≤ 5, or Dobutamine (any dose)</td>
<td>Dopamine &gt; 5, or Epinephrine &lt; 0.1, or Norepinephrine &lt; 0.1</td>
<td>Dopamine &gt; 15 or Epinephrine &gt; 0.1 or Norepinephrine &gt; 0.1</td>
</tr>
<tr>
<td>Renal</td>
<td>&lt; 110 (C)</td>
<td>111-170 (C)</td>
<td>171-290 (C)</td>
<td>300-440 (C) or &lt; 500 (UO)</td>
<td>&gt; 440 (C) or &lt; 200 (UO)</td>
</tr>
</tbody>
</table>

**MANAGEMENT**

**Management during the first week**

Management of necrotizing pancreatitis during the first week of admission consists mainly of frequent clinical evaluation, analgesia and supportive measures. In the first few days after admission, patients should be evaluated for the presence of the systemic inflammatory response syndrome (SIRS). Patients with persisting SIRS have a significantly worse outcome. Monitoring SIRS is an effective bedside tool for assessment of disease progression because measurement of its components can be repeated easily.

In the event of deterioration or absence of clinical improvement at the end of the first week, CECT or MRI is indicated to assess the presence and extent of pancreatic or extrapancreatic necrosis, or extrapancreatic fluid collections. Clinical deterioration during the first week is caused most often by progression of SIRS and seldom because of early infection of pancreatic necrosis. As such, surgical intervention is not indicated during this phase unless an ischaemic or perforated viscus is the cause. If emergency surgery is deemed necessary, it is associated with mortality rates of 40-78 per cent. Early emergency surgery potentially aggravates multiple organ failure, as shown by an increase in APACHE II scores after operation. Additionally, complications (such as bleeding, intestinal fistula) are more prone to occur if surgery is performed before the acute necrotic collection has had time to progress to ‘walled-off’ necrosis. Although there is no compelling evidence to support either of these arguments, the unfavourable outcomes following early debridement have driven
clinicians towards more conservative policies in the early phase of the disease.

**Pain control**

Analgesics, graded according to pain severity, must be provided for all patients in routine clinical practice; in this setting, it has been found that analgesics are graded according to the severity of the pain; patients with mild acute pancreatitis received mainly NSAIDs and tramadol whereas patients with severe pancreatitis received a high percentage of opioids or an association of analgesics including NSAIDs, tramadol and opioids. It is quite surprising that, in a disease such as acute pancreatitis in which the pain represents the main symptom at onset, there is limited information regarding the best therapeutic approach to pain. A meta-analysis taking into consideration eight randomized controlled trials including 356 patients showed that compared with procaine, pentazocine lowered the severity of pain, thus decreasing the necessity for additional analgesics. In addition, a combination of fentanyl, atropine, droperidol and lidocaine rendered a lower pain score and patients treated with metamizole tended to have less pain than those treated with morphine; it should be pointed out that the randomized controlled trials comparing different analgesics were of low quality. Another metaanalytic study evaluated the effectiveness and safety of opioids for treating acute pancreatitis pain. This meta-analysis involved five RCTs with a total of 227 patients having acute pancreatitis pain. The opioids assessed were intravenous and intramuscular buprenorphine, intramuscular pethidine, intravenous pentazocine, transdermal fentanyl and subcutaneous morphine. Opioids may be an appropriate choice in the treatment of acute pancreatitis pain and, compared to other analgesic options, opioids decrease the need for supplementary analgesia. However, once again, mainly due to small numbers of patients enrolled, the findings of this review are limited by the lack of information as to a full appraisal of the risk of bias and the measurement of relevant outcomes. Additional studies on this topic are indicated in the near future.

**Fluid resuscitation**

Fluid resuscitation aims at counteracting the effects of hypovolaemia due to ‘third spacing’, and is directed at restoring the microcirculation and thereby oxygenation of the pancreas and other organ systems. Adequate fluid resuscitation may prevent further local injury to the pancreas and so might inhibit the systemic inflammatory response. Traditionally, liberal intravenous fluid infusion has been advocated. The patient’s vital signs (heart rate, blood pressure, oxygen saturation) and urinary output (accepted minimum urinary output over 0-5ml per kg bodyweight per h) are monitored, taking into account pre-existing conditions contraindicating high-volume fluid infusion. Fluid resuscitation is especially important in the first 12-24 h after admission. Thereafter, the amount of fluid administered can be decreased.

**Role of endoscopic retrograde cholangiopancreatography**

In gallstone pancreatitis, obstructing stones or biliary sludge usually pass through the biliary tract spontaneously. Obstruction persists in some patients, increasing the risk of developing cholangitis. If progressive cholestasis and dilatation of the common bile duct is accompanied by fever, cholangitis should be suspected and urgent endoscopic retrograde cholangiopancreatography (ERCP) with
sphincterotomy is indicated. The benefit of ERCP in patients with pancreatitis without cholangitis, however, is unclear.

Specific drugs

Regarding somatostatin and its long-acting analogue octreotide, it has been shown in the only trial using a correct methodological approach that octreotide at a dosage of 0.1 and 0.2 mg t.i.d is not able to reduce mortality, the rate of newly-developed complications, the duration of pain, surgical interventions or the length of the hospital stay. These data have also been confirmed by a meta-analysis showing that octreotide does not reduce surgical interventions, sepsis, mortality or overall complication rates.

Platelet activating factor antagonists have ameliorated acute pancreatitis in humans by two phase II randomized trials involving a total of 133 patients with acute pancreatitis who showed significant improvement in organ failure scores. However, a randomized, lexipafant had no effect on new organ failure during treatment.

Nutrition

In necrotizing pancreatitis, adequate nutritional intake can be obtained through an oral diet or enteral nutrition. Several meta-analyses of randomized trials comparing enteral with parenteral nutrition showed that enteral nutrition significantly reduces organ failure, infections and mortality. No differences were found between different types of enteral nutrition formulation. Enteral feeding is hypothesized to maintain the integrity of the gastrointestinal mucosal barrier, thus inhibiting bacterial translocation and reducing infectious complications.

Antibiotic prophylaxis

Secondary infection of pancreatic or extrapancreatic necrosis occurs in approximately one-third of patients with necrotizing pancreatitis. In the first week after admission, there is no role for routine antibiotic prophylaxis in the treatment of necrotizing pancreatitis. Antibiotics should be withheld until infection is proven with positive cultures. In most patients, infection of pancreatic or extrapancreatic necrosis does not occur until week 3 or 4. Antimicrobial agents with favourable pancreatic tissue penetration, such as carbapenems, metronidazole and quinolones, are recommended.

Continuous regional artery infusion (CRAI) with antibiotics and proteases inhibitors in SAP improved the effects of both local and systemic inflammatory response.

Probiotics

Even if an early study showed that probiotics administered for 1 week by nasojejunal tube were effective in reducing pancreatic sepsis and the number of surgical interventions related to pancreatic damage, a subsequent multicenter study on predicted severe pancreatitis yielded disappointing results on the clinical usefulness of probiotics. In fact, a probiotic prophylaxis does not reduce the risk of infectious complications and is associated with an increased risk in mortality; the main complication of probiotic treatment was bowel ischemia.

Antioxidants
Several substances, such as alpha tocopherol, ascorbic acid, betacarotene, caffeic acid phenethyl ester, carnitine, green tea, melatonin, N-acetylcysteine, resveratrol, quercetin and selenium, alone or in combination, were added to the fluid therapy in human studies to evaluate their usefulness in treating pancreatitis. The results are conflicting; while some authors reported no beneficial effects of an intravenous antioxidant formula comprising selenium, N-acetylcysteine and vitamin C, others found that antioxidant supplementation associated with standard medical treatment may decrease the length of hospital stay and rates of complications in patients with acute pancreatitis. In conclusion, there are insufficient clinical data to support the use of antioxidants alone or in combination together with conventional therapy for the treatment of acute pancreatitis, and double blind, randomized, placebo-controlled clinical trials with a larger sample size are necessary.

Anti-inflammatory agents

Indomethacin, which inhibits phospholipase A2 activity and cyclooxygenase activity thus decreasing neutrophil mediated inflammation, has been clinically studied based on earlier pre-clinical studies. One study assessing this therapy, however, only reported decreased pain and opiate use when given to patients with acute pancreatitis suggesting analgesia but not anti-inflammatory related benefits. So far benefits of indomethacin have been largely limited to post-ERCP pancreatitis.

Steroid therapy is widely used to dampen inflammation in various organ systems. Though steroid therapy has been shown to be beneficial in the treatment of autoimmune pancreatitis, in acute pancreatitis however steroid therapy has been implicated in disease induction. However, given that some pre-clinical studies suggest that steroids can reduce the inflammatory cascade, leukocyte recruitment, and subsequent pancreatic damage when given prophylactically, further well-designed studies are warranted.

Abdominal compartment syndrome

Abdominal compartment syndrome (ACS) is rare in patients with necrotizing pancreatitis and, if the suspicion arises, it occurs most often in the first week after symptom onset. Aggressive fluid resuscitation, retroperitoneal fluid accumulation and ascites may contribute to raised intraabdominal pressure (transvesical pressure measurements exceeding 12 mmHg). Persisting intraabdominal hypertension is believed to be a precursor of ACS. The World Society of the Abdominal Compartment Syndrome defines ACS as ‘persisting abdominal pressure above 20 mmHg accompanied by new onset organ failure’.

Several non-invasive strategies may aid in reducing the intra-abdominal pressure: enteral decompression through gastric or rectal tubes, recalibrating the intravenous fluid regimen for a zero-to-negative balance, and increasing abdominal wall compliance through medication. If non-invasive options are not sufficiently effective, the next step of treatment should be aimed at evacuation of excess intra-abdominal or retroperitoneal free fluids, such as ascites, by percutaneous catheter drainage (PCD).

Decompression laparotomy is sometimes applied as a ‘last resort’ if multiple
organ failure escalates. However, currently there is no evidence that surgical decompression has a beneficial effect on outcome. If there is no infected necrosis (as in most patients during the first week after admission) the retroperitoneum should not be opened during this procedure to minimize the risk of introducing pathogens.

Although decompression laparotomy seems effective in individuals without pancreatitis, ACS in patients with pancreatitis seems associated mainly with massive fluid resuscitation. In these patients, no improvement in overall morbidity and mortality has been documented.

**Management during the second and third weeks**

*Infection of pancreatic necrosis*

Infected pancreatic necrosis is usually diagnosed during the second or third week after onset. Other possible sources of infection, such as pneumonia, must be ruled out first, as these tend to occur earlier in the course of the disease. Cross-sectional imaging is indicated to assess the evolution of pancreatic necrosis and peripancreatic fluid collections. Occasionally, CT or MRI may reveal retroperitoneal gas bubbles inside pancreatic fluid collections pathognomonic for infection. These collections rarely show signs of complete encapsulation before the fourth week.

*Fine-needle aspiration*

Fine-needle aspiration (FNA) culture of pancreatic fluid collections is useful if the diagnosis is uncertain, and has the added value of optimizing antibacterial therapy. Routine FNA culture was promoted more widely in the past, but has been used more selectively in recent years. The reason for this shift is that, with the more conservative approach currently advocated, FNA results less often lead to a change in management and so aspiration is indicated less frequently. FNA carries a risk of false-negative results in up to 25 per cent depending on timing after onset and indication. Therefore, FNA should be used to obtain information about a collection only when the result will direct the treatment plan. FNA is warranted, for instance, in patients who fail to recover from organ failure (and thus have persisting high inflammatory parameters so that infected pancreatic necrosis cannot be discriminated clinically) and without signs of infection on CECT. A positive FNA would warrant a step up in treatment of the fluid collection.

*Antifungals*

Fungal infections have increased and now account for 10-20% of the microorganisms involved in infected pancreatic necrosis. Antifungal prophylaxis may be advocated in selected patients, i.e. those having risk factors for fungal infection, such as patients with intravenous catheters for parenteral nutrition and those in whom antibiotics are used for a long period of time. In addition, a fungal prophylaxis in patients operated on for pancreatic necrosis is less convincing. Patients with yeast on Gram’s stain following CT-guided FNA or direct culture during the necrosectomy should receive fluconazole for Candida albicans which is the most common fungal isolate in pancreatic infections. In the case of detection of Candida glabrata, a higher dose of fluconazole or caspofungin should be used. Patients who have been treated
prophylactically with fluconazole and subsequently develop infected necrosis with yeast should be treated with caspofungin.

**Percutaneous catheter drainage**

PCD is an important adjunct in the care of patients with infection of acute necrotic collections or walled-off necrosis. Once infection occurs, the patient must be treated effectively in a timely manner for a good outcome. Most patients need antibiotics and drainage. The use of PCD is the first step of the step-up approach. Catheters are placed optimally by the left or right retroperitoneal route, depending on the anatomy of the collections. In the absence of solid evidence regarding the optimal timing of PCD, different strategies are applied. A positive FNA culture during the second or third week leads to PCD in some institutions, whereas in others antibiotics are started first, with PCD in this disease phase only following further clinical deterioration. Early PCD may substantially improve a patient’s condition but can also introduce infection in a sterile collection, thereby leading to deterioration, so it is important that infection be documented clearly first.

The first step in treatment should be percutaneous or endoscopic drainage, followed by surgical or endoscopic necrosectomy only if clinically necessary.

**Management during the fourth, fifth and sixth weeks**

A second peak in mortality is seen in this phase of the disease, mostly associated with infection of the pancreatic or extrapancreatic necrosis. In general, only patients with infected necrosis should undergo invasive interventions. Interventions such as endoscopic transluminal drainage and necrosectomy, and minimally invasive or open necrosectomy should be delayed if possible to around 4 weeks after the onset of symptoms. This allows the collection to become walled-off, which is believed to facilitate necrosectomy.

**Minimally invasive surgical necrosectomy**

Two minimally invasive surgical techniques have gained widespread acceptance: sinus tract endoscopy (also referred to as minimal access retroperitoneal pancreatic necrosectomy, MARPN) and video-assisted retroperitoneal debridement (VARD). In both procedures, access to the necrotic pancreas is achieved by following the tract of a radiologically placed drainage catheter.

A few case series have been published on laparoscopic necrosectomy. This approach offers access to the lesser sac and simultaneous management of intra-abdominal organs (for example concurrent cholecystectomy). However, it also has the disadvantage of introducing a continuum between the peritoneal cavity and the retroperitoneum containing infected pancreatic tissue.

**Endoscopic transluminal drainage or necrosectomy**

Parallel to the development of minimally invasive surgical strategies, endoscopic transluminal approaches have been developed. Under direct vision or endoscopic ultrasound guidance, the gastric or duodenal wall is punctured to reach the walled-off necrosis. The transluminal tract is dilated sequentially using a balloon. Short pigtail catheter drains or a stent can be used to prevent the access to the retroperitoneum from closing after the first procedure. A nasocystic catheter is placed
in the necrotic cavity for continuous irrigation. The use of multiple transluminal gateways has been suggested to improve drainage of the infected material, and successful drainage without the need for additional interventions was achieved in up to 90 per cent in a small cohort of selected patients. Patients in whom endoscopic drainage proves insufficient may benefit from endoscopic necrosectomy. Like sinus tract endoscopy, the transluminal drain tract is dilated further for introduction of an endoscope. Various instruments are used for the actual necrosectomy, such as endoscopic baskets, snares, jet irrigation and forceps.  

*Open surgical necrosectomy*

Primary open surgical necrosectomy has been the standard treatment of infected necrosis for decades. The classical approach is to enter the retroperitoneum through a laparotomy, after which the necrotic tissue is removed by blunt dissection. Healthy pancreatic tissue is preserved as much as possible, and by doing so the risk of postoperative bleeding or pancreatic fistula is minimized. Different surgical techniques have been developed over the years, such as open packing, closed packing with planned reoperation or postoperative continuous lavage to remove any residual material. Open necrosectomy remains associated with substantial morbidity. These high morbidity rates are generally attributed to the exacerbation of stress induced by the trauma of surgery in an already critically ill patient, but are also closely associated with the timing of intervention and the presence of persistent organ failure. The minimally invasive approaches were developed specifically for this reason, although to date no randomized trial has proven the superiority of minimally invasive techniques over open necrosectomy (or laparotomy).

*Management after the sixth week*

Patients without proof of infection (even after negative FNA culture) who fail to recover, despite prolonged maximal supportive care, are suspected of sustaining a low-grade infection. Patients in whom a sterile fluid collection causes clinically significant morbidity (gastric or biliary outlet obstruction, pain) should be considered for surgical or endoscopic necrosectomy.

Cholecystectomy or, if not deemed feasible, ERCP with sphincterotomy should be considered to minimize the risk of recurrent biliary pancreatitis and other gallstone-related disease. It is generally recommended to postpone intervention until all radiological and biochemical signs of inflammation have subsided.

Finally, several other complications may occur during this phase. Vascular complications may be seen on CECT, such as splenic or portal vein thrombosis or, less commonly, splenic artery pseudoaneurysm. These must be dealt with using appropriate application of anticoagulant therapy, endovascular coiling, stenting or embolization, or sometimes even splenectomy. Pancreatic fistulas to various organs may also occur and can be treated quite successfully by endoscopic papillary stenting, thus facilitating drainage of the pancreatic secretion into the duodenum.
Sterile and Infected Peripancreatic Fluid Collections

The presence of acute abdominal fluid during an episode of AP has been described in 30% to 57% of patients. In contrast to pseudocysts and cystic neoplasias of the pancreas, fluid collections are not surrounded or encased by epithelium or fibrotic capsule. Treatment is supportive because most fluid collections will be spontaneously reabsorbed by the peritoneum. The presence of fever, elevated white
blood cell (WBC) count, and abdominal pain suggest infection of this fluid and percutaneous aspiration is confirmatory. Percutaneous drainage and IV administration of antibiotics should be instituted if infection is present.

**Pancreatic Necrosis and Infected Necrosis**

Pancreatic necrosis is the presence of nonviable pancreatic parenchyma or peripancreatic fat; it can present as a focal area or diffuse involvement of the gland. Contrast-enhanced CT is the most reliable technique to diagnose pancreatic necrosis. It is typically seen as areas of low attenuation (<40 to 50 HU) after the injection of IV contrast. Normal parenchyma usually has a density of 100 to 150 HU. Up to 20% of patients with AP develop pancreatic necrosis. It is important to identify and provide proper treatment of this complication because most patients who develop multiorgan failure have necrotizing pancreatitis; pancreatic necrosis has been documented in up to 80% of the autopsies of patients who died after an episode of AP.

The main complication of pancreatic necrosis is infection. The risk is directly related to the amount of necrosis; in patients with pancreatic necrosis involving less than 30% of the gland, the risk of infection is 22%. The risk is 37% for patients with pancreatic necrosis that involves 30% to 50% of the gland and up to 46% if more than 70% of the gland is affected. This complication is associated with bacterial translocation usually involving enteric flora, such as gram-negative rods (e.g., *Escherichia coli*, *Klebsiella* and *Pseudomonas* spp.) and *Enterococcus* spp.

Infected pancreatic necrosis should be suspected in patients with prolonged fever, elevated WBC count, or progressive clinical deterioration. Evidence of air within the pancreatic necrosis seen on a CT scan confirms the diagnosis but is a rare finding.

If infected necrosis is suspected, fine-needle aspiration (FNA) should be performed. A positive Gram stain and/or culture establish the diagnosis. Although positive cultures are confirmatory, a recent review has demonstrated that despite negative preoperative cultures, 42% of patients with so-called persistent unwellness will have infected necrosis.

Once infection has been demonstrated, IV antibiotics should be given. Because of their penetration into the pancreas and spectrum coverage, carbapenems are the first option of treatment. Alternative therapy includes quinolones, metronidazole, third-generation cephalosporins, and piperacillin.

Definitive treatment for infected pancreatic necrosis is surgical debridement with necrosectomy, closed continuous irrigation, and open packaging. The overall mortality rate after open necrosectomy is 25% to 30%. Outcomes are time dependent, with patients who undergo surgery in the first 14 days having a mortality rate of 75%; those who undergo surgery between 15 and 29 days and after 30 days have mortality rates of 45% and 8%, respectively. As a result of the elevated morbidity and mortality rates with open debridement, endoscopic and laparoscopic techniques are being used more often.

**Pancreatic Pseudocysts**
Pancreatic pseudocysts occur in 5% to 15% of patients who have peripancreatic fluid collections after AP. By definition, the capsule of a pseudocyst is composed of collagen and granulation tissue and it is not lined by epithelium. The fibrotic reaction typically requires at least 4 to 8 weeks to develop.

Up to 50% of patients with pancreatic pseudocysts will develop symptoms. The presence of persistent pain, early satiety, nausea, weight loss, and elevated pancreatic enzyme levels in plasma suggest this diagnosis. The diagnosis is corroborated with by CT or MRI. EUS with FNA is indicated for patients in whom the diagnosis of pancreatic pseudocyst is not clear. Characteristic features of pancreatic pseudocysts include high amylase levels associated with the absence of mucin and low carcinoembryonic antigen (CEA) levels.

Observation is indicated for asymptomatic patients because spontaneous regression has been documented in up to 70% of cases; this is particularly true for patients with pseudocysts smaller than 4 cm in diameter, located in the tail, and no evidence of pancreatic duct obstruction or communication with the main pancreatic duct. Invasive therapies are indicated for symptomatic patients or when the differentiation between a cystic neoplasm and pseudocyst is not possible. Because most patients are treated with decompressive procedures and not with resection, it is imperative to have a pathologic diagnosis. Surgical drainage has been the traditional approach for pancreatic pseudocysts. However, there is increasing evidence that transgastric and transduodenal endoscopic drainage are safe and effective approaches for patients with pancreatic pseudocysts in close contact (defined as <1 cm) with the stomach and duodenum, respectively. In addition, transpapillary drainage can be attempted in pancreatic pseudocysts communicating with the main pancreatic duct. For patients in whom a pancreatic duct stricture is associated with a pancreatic pseudocyst, endoscopic dilation and stent placement are indicated.

Surgical drainage is indicated for patients with pancreatic pseudocysts that cannot be treated with endoscopic techniques and patients who fail endoscopic treatment. Definitive treatment depends on the location of the cyst. Pancreatic pseudocysts closely attached to the stomach should be treated with a cystgastrostomy. In this procedure, an anterior gastrostomy is performed. Once the pseudocyst is located, it is drained through the posterior wall of the stomach using a linear stapler. The defect in the anterior wall of the stomach is closed in two layers. Pancreatic pseudocysts located in the head of the pancreas that are in close contact with the duodenum are treated with a cystoduodenostomy. Finally, some pseudocysts are not in contact with the stomach or duodenum. The surgical treatment for these patients is a Roux-en-Y cystojejunostomy. Surgical cyst-enterostomy is successful in achieving immediate cyst drainage in over 90% of cases. Following initial resolution, recurrent pseudocyst formation may occur in up to 12% of cases during long-term follow-up, depending on the location of the cyst and underlying cause of the disease.

Complications of pancreatic pseudocysts include bleeding and pancreaticopleural fistula secondary to vascular and pleural erosion, respectively, bile duct and duodenal obstruction, rupture into the abdominal cavity, and infection.
Percutaneous drainage is only indicated for septic patients secondary to pseudocyst infection because it has a high incidence of external fistula.

Pancreatic Ascites and Pancreaticopleural Fistulas

Although very rare, complete disruption of the pancreatic duct can lead to significant accumulation of fluid. This condition should be suspected in patients who have an episode of AP, develop significant abdominal distention, and have free intraabdominal fluid. Diagnostic paracentesis typically demonstrates elevated amylase and lipase levels. Treatment consists of abdominal drainage combined with endoscopic placement of a requires surgical treatment; it consists of distal resection and closure of the proximal stump.

Posterior pancreatic duct disruption into the pleural space has been described rarely. Symptoms that suggest this condition include dyspnea, abdominal pain, cough, and chest pain. The diagnosis is confirmed with chest x-ray, thoracentesis, and CT scan. Amylase levels above 50,000 IU in the pleural fluid confirm the diagnosis. It is more common after alcoholic pancreatitis and, in 70% of patients, is associated with pancreatic pseudocysts. Initial treatment requires chest drainage, parenteral nutritional support, and administration of octreotide. Up to 60% of patients respond to this therapy. Persistent drainage should also be treated with endoscopic sphincterotomy and stent placement. Patients who do not respond to these measures require surgical treatment, similar to that described for pancreatic ascites.

Vascular Complications

Acute pancreatitis is rarely associated with arterial vascular complications. The most common vessel affected is the splenic artery, but the superior mesenteric, cystic, and gastroduodenal arteries have also been found to be affected. It has been proposed that pancreatic elastase damages the vessels, leading to pseudoaneurysm formation. Spontaneous rupture results in massive bleeding. Clinical manifestations include sudden onset of abdominal pain, tachycardia, and hypotension. If possible, arterial embolization should be attempted to control the bleeding. Refractory cases require ligation of the vessel affected. The mortality ranges from 28% to 56%.

Pancreatic inflammation can also produce vascular thrombosis; the vessel usually affected is the splenic vein but, in severe cases, it can extend into the portal venous system. Imaging demonstrates splenomegaly, gastric varices, and splenic vein occlusion. Thrombolytics have been described in the acute early phase; however, most patients can be managed with conservative treatment. Recurrent episodes of upper gastrointestinal bleeding caused by venous hypertension should be treated with splenectomy.

Pancreatocutaneous Fistula

The frequency of pancreatic fistulas is low. Only 0.4% of patients develop this complication after an acute episode. However, the incidence of these complications
increases in patients with other complications after AP—4.5% in patients with pancreatic pseudocysts (4.5%) and 40% in patients with infected necrosis after surgical debridement. Treatment is conservative for most patients.

IAP/APA ACUTE PANCREATITIS GUIDELINES (2013)

A. Diagnosis of acute pancreatitis and etiology

1. The definition of acute pancreatitis is based on the fulfillment of ‘2 out of 3’ of the following criteria: clinical (upper abdominal pain), laboratory (serum amylase or lipase >3x upper limit of normal) and/or imaging (CT, MRI, ultrasonography) criteria. (GRADE 1B, strong agreement)

2. On admission, the etiology of acute pancreatitis should be determined using detailed personal (i.e. previous acute pancreatitis, known gallstone disease, alcohol intake, medication and drug intake, known hyperlipidemia, trauma, recent invasive procedures such as ERCP) and family history of pancreatic disease, physical examination, laboratory serum tests (i.e. liver enzymes, calcium, triglycerides), and imaging (i.e. right upper quadrant ultrasonography). (GRADE 1B, strong agreement)

3. In patients considered to have idiopathic acute pancreatitis, after negative routine work-up for biliary etiology, endoscopic ultrasonography (EUS) is recommended as the first step to assess for occult microlithiasis, neoplasms and chronic pancreatitis. If EUS is negative, (secretin-stimulated) MRCP is advised as a second step to identify rare morphologic abnormalities. CT of the abdomen should be performed. If etiology remains unidentified, especially after a second attack of idiopathic pancreatitis, genetic counseling (not necessarily genetic testing) should be considered. (GRADE 2C, weak agreement)

B. Prognostication/prediction of severity

4. Systemic inflammatory response syndrome (SIRS) is advised to predict severe acute pancreatitis at admission and persistent SIRS at 48 hours. (GRADE 2B, weak agreement)

5. During admission, a 3-dimension approach is advised to predict outcome of acute pancreatitis combining host risk factors (e.g. age, co-morbidity, body mass index), clinical risk stratification (e.g. persistent SIRS) and monitoring response to initial therapy (e.g. persistent SIRS, blood urea nitrogen, creatinine). (GRADE 2B, strong agreement)

C. Imaging

6. The indication for initial CT assessment in acute pancreatitis can be: 1) diagnostic uncertainty, 2) confirmation of severity based on clinical predictors of severe acute pancreatitis, or 3) failure to respond to conservative treatment or in the setting of clinical deterioration. Optimal timing for initial CT assessment is at least 72-96 hours after onset of symptoms. (GRADE 1C, strong agreement)

7. Follow up CT or MR in acute pancreatitis is indicated when there is a lack of clinical improvement, clinical deterioration, or especially when invasive intervention is considered. (GRADE 1C, strong agreement)
8. It is recommended to perform multidetector CT with thin collimation and slice thickness (i.e. 5mm or less), 100-150 ml of non-ionic intra-venous contrast material at a rate of 3mL/s, during the pancreatic and/or portal venous phase (i.e. 50-70 seconds delay). During follow up only a portal venous phase (monophasic) is generally sufficient. For MR, the recommendation is to perform axial FS-T2 and FS-T1 scanning before and after intravenous gadolinium contrast administration.(GRADE 1C, strong agreement)

D. Fluid therapy
9. Ringer’s lactate is recommended for initial fluid resuscitation in acute pancreatitis.(GRADE 1B, strong agreement)
10a. Goal directed intravenous fluid therapy with 5-10 ml/kg/h should be used initially until resuscitation goals are reached.(GRADE 1B, weak agreement)
10b. The preferred approach to assessing the response to fluid resuscitation should be based on one or more of the following: 1) non-invasive clinical targets of heart rate < 120/min, mean arterial pressure between 65-85 mmHg (8.7-11.3 kPa), and urinary output > 0.5-1ml/kg/h, 2) invasive clinical targets of stroke volume variation, and intrathoracic blood volume determination, and 3) biochemical targets of hematocrit 35-44%.(GRADE 2B, weak agreement)

E. Intensive care management
11. Patients diagnosed with acute pancreatitis and one or more of the parameters identified at admission as defined by the guidelines of the Society of Critical Care Medicine (SCCM). Furthermore, patients with severe acute pancreatitis as defined by the revised Atlanta Classification (i.e. persistent organ failure) should be treated in an intensive care setting.(GRADE 1C, strong agreement)
12. Management in, or referral to, a specialist center is necessary for patients with severe acute pancreatitis and for those who may need interventional radiologic, endoscopic, or surgical intervention.(GRADE 1C, strong agreement)
13. A specialist center in the management of acute pancreatitis is defined as a high volume center with up-to-date intensive care facilities including options for organ replacement therapy, and with daily (i.e. 7 days per week) access to interventional radiology, interventional endoscopy with EUS and ERCP assistance as well as surgical expertise in managing necrotizing pancreatitis. Patients should be enrolled in prospective audits for quality control issues and into clinical trials whenever possible.(GRADE 2C, weak agreement)
14. Early fluid resuscitation within the first 24 hours of admission for acute pancreatitis is associated with decreased rates of persistent SIRS and organ failure.(GRADE 1C, strong agreement)
15. Abdominal compartment syndrome (ACS) is defined as a sustained intra-abdominal pressure > 20 mmHg that is associated with new onset organ failure.(GRADE 2B, strong agreement)
16. Medical treatment of ACS should target 1) hollow-viscera volume, 2) intra/extra vascular fluid and 3) abdominal wall expansion. Invasive treatment should only be used after multidisciplinary discussion in patients with a sustained intra-abdominal pressure >25mmHg with new onset organ failure refractory to
medical therapy and nasogastric/rectal decompression. Invasive treatment options include percutaneous catheter drainage of ascites, midline laparostomy, bilateral subcostal laparostomy, or subcutaneous linea alba fasciotomy. In case of surgical decompression, the retroperitoneal cavity and the omental bursa should be left intact to reduce the risk of infecting peripancreatic and pancreatic necrosis.(GRADE 2C, strong agreement)

F. Preventing infectious complications
17. Intravenous antibiotic prophylaxis is not recommended for the prevention of infectious complications in acute pancreatitis.(GRADE 1B, strong agreement)
18. Selective gut decontamination has shown some benefits in preventing infectious complications in acute pancreatitis, but further studies are needed.(GRADE 2B, weak agreement)
19. Probiotic prophylaxis is not recommended for the prevention of infectious complications in acute pancreatitis.(GRADE 1B, strong agreement)

G. Nutritional support
20. Oral feeding in predicted mild pancreatitis can be restarted once abdominal pain is decreasing and inflammatory markers are improving.(GRADE 2B, strong agreement)
21. Enteral tube feeding should be the primary therapy in patients with predicted severe acute pancreatitis who require nutritional support.(GRADE 1B, strong agreement)
22. Either elemental or polymeric enteral nutrition formulations can be used in acute pancreatitis.(GRADE 2B, strong agreement)
23. Enteral nutrition in acute pancreatitis can be administered via either the nasojejunal or nasogastric route.(GRADE 2A, strong agreement)
24. Parenteral nutrition can be administered in acute pancreatitis as second-line therapy if nasojejunal tube feeding is not tolerated and nutritional support is required.(GRADE 2C, strong agreement)

H. Biliary tract management
25. ERCP is not indicated in predicted mild biliary pancreatitis without cholangitis.(GRADE 1A, strong agreement). ERCP is probably not indicated in predicted severe biliary pancreatitis without cholangitis (GRADE 1B, strong agreement). ERCP is probably indicated in biliary pancreatitis with common bile duct obstruction (GRADE 1C, strong agreement) ERCP is indicated in patients with biliary pancreatitis and cholangitis (GRADE 1B, strong agreement)
26. Urgent ERCP (<24 hrs) is required in patients with acute cholangitis. Currently, there is no evidence regarding the optimal timing of ERCP in patients with biliary pancreatitis without cholangitis.(GRADE 2C, strong agreement)
27. MRCP and EUS may prevent a proportion of ERCPs that would otherwise be performed for suspected common bile duct stones in patients with biliary pancreatitis who do not have cholangitis, without influencing the clinical course. EUS is superior to MRCP in excluding the presence of small (<5mm) gallstones. MRCP is less
invasive, less operator-dependent and probably more widely available than EUS. Therefore, in clinical practice there is no clear superiority for either MRCP or EUS.(GRADE 2C, strong agreement)

I. Indications for intervention in necrotizing pancreatitis

28. Common indications for intervention (either radiological, endoscopical or surgical) in necrotizing pancreatitis are: 1) Clinical suspicion of, or documented infected necrotizing pancreatitis with clinical deterioration, preferably when the necrosis has become walled-off, 2) In the absence of documented infected necrotizing pancreatitis, ongoing organ failure for several weeks after the onset of acute pancreatitis, preferably when the necrosis has become walled-off.(GRADE 1C, strong agreement)

29. Routine percutaneous fine needle aspiration of peripancreatic collections to detect bacteria is not indicated, because clinical signs (i.e. persistent fever, increasing inflammatory markers) and imaging signs (i.e. gas in peripancreatic collections) are accurate predictors of infected necrosis in the majority of patients. Although the diagnosis of infection can be confirmed by fine needle aspiration (FNA), there is a risk of false-negative results.(GRADE 1C, strong agreement)

30. Indications for intervention (either radiological, endoscopical or surgical) in sterile necrotizing pancreatitis are: 1) Ongoing gastric outlet, intestinal, or biliary obstruction due to mass effect of walled-off necrosis (i.e. arbitrarily >4-8 weeks after onset of acute pancreatitis), 2) Persistent symptoms (e.g. pain, ‘persistent unwellness’) in patients with walled-off necrosis without signs of infection (i.e. arbitrarily >8 weeks after onset of acute pancreatitis), 3) Disconnected duct syndrome (i.e. full transection of the pancreatic duct in the presence of pancreatic necrosis) with persisting symptomatic (e.g. pain, obstruction) collection(s) with necrosis without signs of infections (i.e. arbitrarily >8 weeks after onset of acute pancreatitis).(GRADE 2C, strong agreement)

J. Timing of intervention in necrotizing pancreatitis

31. For patients with proven or suspected infected necrotizing pancreatitis, invasive intervention (i.e. percutaneous catheter drainage, endoscopic transluminal drainage/necrosectomy, minimally invasive or open necrosectomy) should be delayed where possible until at least 4 weeks after initial presentation to allow the collection to become ‘walled-off’. (GRADE 1C, strong agreement)

32. The best available evidence suggests that surgical necrosectomy should ideally be delayed until collections have become walled-off, typically 4 weeks after the onset of pancreatitis, in all patients with complications of necrosis. No subgroups have been identified that might benefit from earlier or delayed intervention.(GRADE 1C, strong agreement)

K. Intervention strategies in necrotizing pancreatitis

33. The optimal interventional strategy for patients with suspected or confirmed infected necrotizing pancreatitis is initial image-guided percutaneous (retroperitoneal) catheter drainage or endoscopic transluminal drainage,
followed, if necessary, by endoscopic or surgical necrosectomy. (GRADE 1A, strong agreement)

34. Percutaneous catheter or endoscopic transmural drainage should be the first step in the treatment of patients with suspected or confirmed (walled-off) infected necrotizing pancreatitis. (GRADE 1A, strong agreement)

35. There are insufficient data to define subgroups of patients with suspected or confirmed infected necrotizing pancreatitis who would benefit from a different treatment strategy. (GRADE 2C, strong agreement)

L. Timing of cholecystectomy (or endoscopic sphincterotomy)

36. Cholecystectomy during index admission for mild biliary pancreatitis appears safe and is recommended. Interval cholecystectomy after mild biliary pancreatitis is associated with a substantial risk of readmission for recurrent biliary events, especially recurrent biliary pancreatitis. (GRADE 1C, strong agreement)

37. Cholecystectomy should be delayed in patients with peripancreatic collections until the collections either resolve or if they persist beyond 6 weeks, at which time cholecystectomy can be performed safely. (GRADE 2C, strong agreement)

38. In patients with biliary pancreatitis who have undergone sphincterotomy and are fit for surgery, cholecystectomy is advised, because ERCP and sphincterotomy prevent recurrence of biliary pancreatitis but not gallstone related gallbladder disease, i.e. biliary colic and cholecystitis. (GRADE 2B, strong agreement)

VI. Plan and structure of class

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<td>Questions, II level</td>
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<td>MCQs Typical clinical cases, II level MCQ</td>
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<td>II</td>
<td>Clinical cases, MCQs</td>
<td>MCQs Typical clinical cases, II level MCQ</td>
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### Main stage

**Formation of students professional skills:**

1. Master the skills of the physical examination
2. Perform physical examination of the patient with acute pancreatitis
3. Plan the patients laboratory and instrumental examinations
4. Differential diagnosis
5. Treatment schemes

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<td>Practical training</td>
<td>Patients with acute pancreatitis, patients cards</td>
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<td>Practical training</td>
<td>Clinical cases, III level MCQs</td>
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<td>Practical training</td>
<td>Diagnostic algorithms, clinical cases with severe and complicated disease</td>
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<td>Practical training</td>
<td>Typical and atypical clinical cases</td>
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### Final stage

**Correction of the professional skills and abilities**

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<td>III</td>
<td>Personal skills control, analysis and evaluation of the results of clinical work, clinical cases, level III MCQs</td>
<td>Clinical cases and III level MCQs</td>
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95 min.

30 min.
### VII. Materials for classes

**Questions** ($\alpha = I$, $\beta = II$)
1. Etiology and pathogenesis of AP.
2. Classification of AP.
3. Clinical signs of AP.
4. Laboratory diagnosis and prognostic scores of AP.
5. Role of localization procedures in diagnosing of AP.
6. Differential diagnosis of AP.
7. Treatment on different stages of AP.

**MCQs** ($\alpha = II$)
1. Which ethiological factors causes acute pancreatitis most oftenly?
   - A. Abdominal trauma, alimentary factor;
   - B. Gallstones, alcohol;
   - C. Hypercalcemia, hyperlipidemia;
   - D. Drugs, toxins;
   - E. ERCP, sphincter of Oddi disfunction.
   Correct answer: B.

2. What instrumental examination should be performed to diagnose necrotizing pancreatitis?
   - A. US;
   - B. ECRP;
   - C. Plain abdominal film;
   - D. Blood gases;
   - E. CT.
   Correct answer: E.

3. The severity and prognosis for patient with acute pancreatitis can be estimated with:
Typical clinical cases (α =II)

1. A 52-year-old male, without alcohol history, admitted to hospital with acute pain in epigastrium, radiating to the back. Amylase level elevated. Which radiological findings (plain abdominal film) will help to diagnose acute pancreatitis?
   Answer: Stomach shifted anteriorly on contrast examination of GIT; air in the duodenal C-loop; colon cutoff sign, which represents distention of the colon to the transverse colon with a paucity of gas distal to the splenic flexure.

2. A 45-year-old male admitted to the surgical department with severe pain in epigastrium with irradiation to the back, which develops after alcohol consumption. Acute pancreatitis was diagnosed. The patient was performed CT scan: pancreatic enlargement. What is the stage of acute pancreatitis according to CT picture (Balthazar score)?
   Answer: Grade B.

3. A 60-year-old female treated in surgical department for acute pancreatitis. On 30 day of treatment in epigastrium appeared mass 10 cm in diameter. CBC: RBC – 3,7*10^{12}/l, WBC – 10*10^9/l. US examination: fluid collected near the head of the pancreatic gland. What complication of acute pancreatitis developed in this case?
   Answer: Postnecrotic pseudocyst.
Atypical clinical cases ($\alpha = \text{III}$)

1. A 40-year-old alcoholic male is admitted with severe epigastric pain radiating to the back. Serum amylase level is reported as normal (fluoroscopic method), but serum lipase is elevated. The serum is noted to be milky in appearance. A diagnosis of pancreatitis is made. The serum amylase is normal because?

**Answer:** The patient has hyperlipidemia.

**VIII. Literature**