Acute pancreatitis

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Acute pancreatitis is an inflammatory disease of the pancreas. Acute abdominal pain is the most common symptom, and increased concentrations of serum amylase and lipase confirm the diagnosis. Pancreatic injury is mild in 80% of patients, who recover without complications. The remaining patients have a severe disease with local and systemic complications. Gallstone migration into the common bile duct and alcohol abuse are the most frequent causes of pancreatitis in adults. About 15–25% of pancreatitis episodes are of unknown origin. Treatment of mild disease is supportive, but severe episodes need management by a multidisciplinary team including gastroenterologists, interventional radiologists, intensivists, and surgeons. Improved understanding of pathophysiology and better assessments of disease severity should ameliorate the management and outcome of this complex disease.

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Introduction

In 1856, Claude Bernard suggested that bile reflux into the common pancreatic duct was the trigger that caused acute pancreatitis.[1] Several subsequent studies led to theories fuelling the debate until 1901, when Eugene Opie proposed that gallstone migration into the common bile duct was the main cause of acute pancreatitis.[2] His conclusion was based on two autopsies of young patients in whom he found a gallstone occluding the orifice of the pancreatic duct. Since then, many other causes of pancreatitis have been discovered, and here we aim to review the clinical and therapeutic aspects of acute pancreatitis.

Epidemiology

The incidence of acute pancreatitis has increased in the past two decades.[3–6] Between 1994 and 2001, the incidence of first-time attack in California increased from 33 to 44 per 100 000 adults,[7] and at present acute pancreatitis accounts for more than 200 000 hospital admissions every year in the USA.[8] Such increase is also seen in European countries.[9] In 80% of patients, acute pancreatitis is mild and resolves without serious morbidity, but in up to 20%, acute pancreatitis is complicated by substantial morbidity and mortality.[10,11] However, the frequency of severe pancreatitis remained stable over time in the USA[7] and European countries.[9] In California, from 1994 to 2001, about 4% of patients died within 92 days after admission, half of whom did so within 14 days.[7] Most late deaths arose from multiple organ dysfunction secondary to infected pancreatic necrosis. Causation of acute pancreatitis defines its epidemiology. Biliary stone migration is more frequent and alcohol abuse is less frequent in women than in men.[7,9,12,13] However, causes are related to risk factors (such as alcohol abuse) that might vary between countries and over time in every country.[9] In children, the main triggers of acute pancreatitis are trauma, systemic diseases, infections, and drugs, whereas genetic causes are rare.[14,15]

Search strategy and selection criteria

We used the PubMed database to search with the terms "acute pancreatitis" together with "complications", "death", "treatment", "sphincterotomy", "antibiotic prophylaxis", and "enteral nutrition". We selected citations from articles in English, German, and French from the past 5 years, but did not exclude commonly referenced and highly cited older publications. We also searched relevant citation lists in selected papers. Several review articles or book chapters were included because they provide comprehensive overviews that are beyond the scope of this Seminar. For treatment and antibiotic prophylaxis of the disease, we focused on randomised controlled trials whenever available.

Pathophysiology

Although controversial, most investigators believe that acute pancreatitis is caused by the unregulated activation of trypsin within pancreatic acinar cells (figure 1). Enzyme activation within the pancreas leads to the autodigestion of the gland and local inflammation. The main factors that trigger acute disease are pancreatic hyperstimulation (mainly seen in experimental models), gallstones, and alcohol abuse. Acute pancreatitis arises when intracellular protective mechanisms to prevent trypsinogen activation or reduce trypsin activity are overwhelmed. These protective mechanisms include the synthesis of trypsin as inactive enzyme trypsinogen, autolysis of activated trypsin, enzyme compartmentalisation, synthesis of specific trypsin inhibitors such as serine protease inhibitor Kazal type 1 (SPINK1), and low intracellular ionised Ca^{2+} concentrations.

After activation of trypsinogen into active trypsin within acinar cells, several enzymes, such as elastase and phospholipase A2, and the complement and kinin pathways are activated.[16] Additionally, inflammation is initiated with local production of mediators such as interleukin 1, interleukin 6, and interleukin 8 from neutrophils, macrophages, and lymphocytes. Tumour necrosis factor α is also released by local macrophages within pancreatic tissue and its production correlates with severity of the experimental disease.[17] Anti-inflammatory cytokines, such as interleukin 10, decrease the severity of experimental pancreatitis.[18]

In addition to these events, activation of endothelial cells enables the transendothelial migration of leucocytes, which release other harmful enzymes.[19] Decreased oxygen delivery to the organ and generation

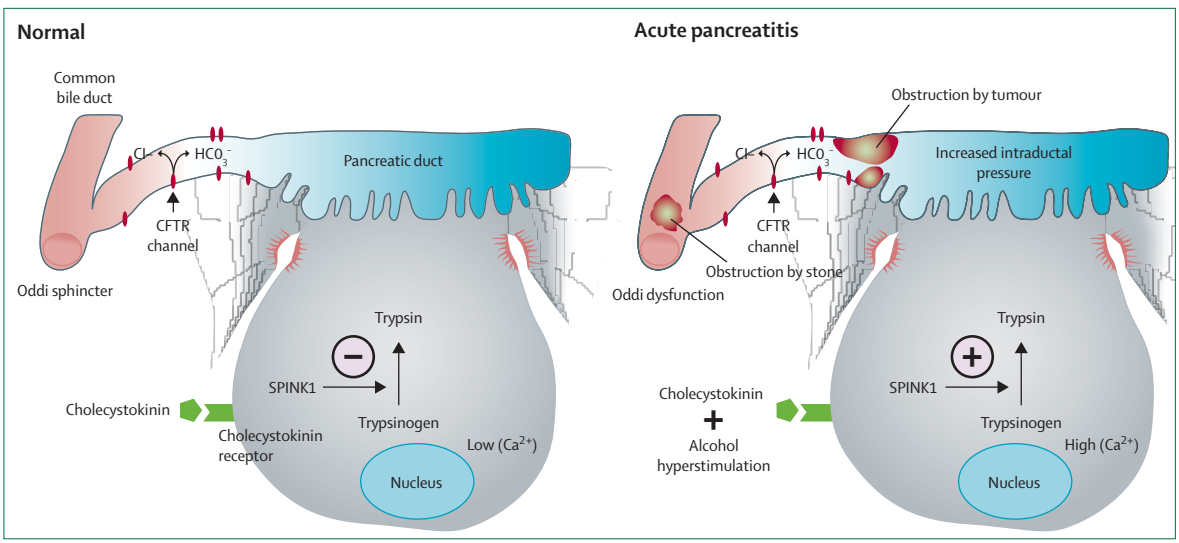

Figure 1: **Pathophysiology of acute pancreatitis**

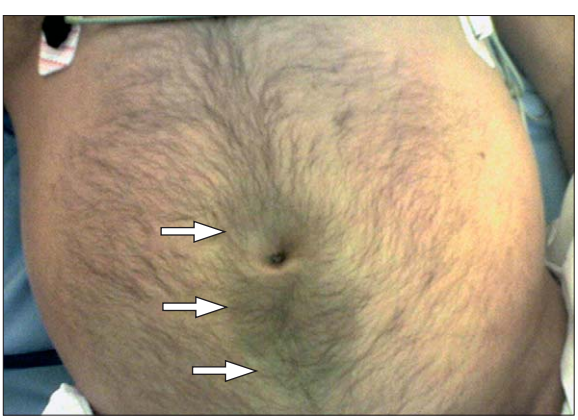

Figure 2: **Exudates (arrows) from pancreatic necrotic areas**

of oxygen-derived free radicals also contribute to injury.[20] Thus, irrespective of the initial factor that triggers the disease, severity of pancreatic damage is related to injury of acinar cells and to activation of inflammatory and endothelial cells. Then, local complications (acinar cell necrosis, pseudocyst formation, and abscess) might develop, and injury in remote organs (ie, lungs) might follow the release of several mediators from the pancreas or from extrapancreatic organs such as the liver.[21]

Diagnosis

Acute pancreatitis is characterised by the presence of acute and constant pain in the epigastric area or the right upper quadrant.[22–24] Pain might last for several days, radiate to the back, and be associated with nausea and vomiting. Physical findings depend on severity of the disease. In mild disease, abdominal palpation reveals tenderness in the upper abdomen. Exudates from pancreatic necrotic areas tracking along the falciform ligament and into the retroperitoneum can be seen in the periumbilical region (Cullen's sign; figure 2) and the flanks. Extension of inflammatory exudates from the peripancreatic region to the diaphragm might lead to shallow respiration.

Two enzymes (amylase and lipase) are released from acinar cells during acute pancreatitis, and their concentration in the serum is used to confirm diagnosis.[25] Serum amylase concentrations exceeding three times the normal upper limit support the diagnosis of acute pancreatitis.[26] Amylase concentrations generally rise in the serum within a few hours after the onset of symptoms and return to normal values within 3–5 days. However, amylase activity might remain within normal range on admission in 19% of the patients.[27,28] Also, serum amylase concentrations might be high in the absence of acute pancreatitis in macroamylasaemia (a syndrome characterised by the formation of large molecular complexes between amylase and abnormal immunoglobulins), in patients with decreased glomerular filtration, in diseases of salivary glands, and in extrapancreatic abdominal diseases associated with inflammation, including acute appendicitis, cholecystitis, intestinal obstruction or ischaemia, peptic ulcer, and gynaecological diseases.[29] Thus, when serum amylase concentration is high and clinical presentation is not consistent with acute pancreatitis, the non-pancreatic causes of hyperamylasaemia should be examined. Follow-up, including CT scan examination and repeated amylase measurements, might help.

Serum lipase concentrations remain high for a longer period of time than do amylase concentrations, which is an advantage over amylase measurement in patients with a delayed presentation.[30] Guidelines for the management of acute pancreatitis emphasise this advantage.[31,32] Assays of many other pancreatic enzymes have been assessed during the past 15 years, but none seems to offer better diagnostic value than those of amylase and lipase.

Diagnosis

Abdominal radiography might show localised ileus in severe pancreatitis. In a third of patients, chest radiography shows abnormalities such as elevation of one hemidiaphragm, and pleural effusions, pulmonary infiltrates or both. When abdominal ultrasound is done, bowel gases often mask focal hypoechoic areas within the pancreas.

Contrast-enhanced CT can be done after admission to confirm diagnosis of disease (87–90% sensitivity and 90–92% specificity), or after 4 days to assess local complications such as fluid collections and necrosis,[33] and to score the disease (see later section). MRI identifies necrosis and fluid collections better than does CT scan.[34]

Course and severity

Most episodes of acute pancreatitis are mild and self-limiting, needing only brief hospitalisation. However, 20% of patients develop a severe disease with local and extrapancreatic complications characterised by early development and persistence of hypovolaemia, and multiple organ dysfunction. Thus, close examination to assess early fluid losses, hypovolaemic shock, and symptoms suggestive of organ dysfunction is crucial. Assessment methods such as the sequential organ failure assessment (SOFA) score[35,36] (table 1) help clinicians to assess organ injury. Ascites, ileus, and, more importantly, increased capillary permeability, which conveys fluid accumulation within the interstitium, contribute to the decreased intravascular volume. Renal dysfunction is also a severe complication that results from inadequate fluid resuscitation, septic complications, or both. Incidence of pulmonary complications is high in severe pancreatitis, ranging from 15% to 55%. Severity of pulmonary complications can vary greatly from mild hypoxaemia without clinical or radiological abnormalities to severe acute respiratory distress syndrome.[21,37] Two peaks of pulmonary complications have been seen during the early phase of severe acute pancreatitis.[38] The first peak arises upon admission, and radiological abnormalities have been found in 15% of patients during that time. By day 5, new radiological abnormalities can be seen in an additional 71% of patients. Thereafter, pulmonary injury might result from septic shock and complicate infection of the necrotic pancreas. Other organs might also be affected during acute pancreatitis. By contrast with lung and renal injury, hepatic injury is usually mild during acute pancreatitis but contributes to the systemic inflammatory response.[39]

Pancreatic necrosis is the most severe local complication because it is frequently associated with pancreatic infections. The diffuse or local area of non-viable parenchyma is initially sterile and can become infected by bacteria of gut origin. Mortality in sterile and infected necrosis is 10% and 25%, respectively. Pseudocyst is a collection of pancreatic juice enclosed by a wall of granulation tissue that results from pancreatic duct leakage. Pancreatic abscess consists of a circumscribed collection of pus that arises around a restricted area of pancreatic necrosis.

The severity of acute pancreatitis is classified into five grades (0–4) on unenhanced CT scan, whereas the degree of pancreatic necrosis is measured by contrast-enhanced CT scan. The sum of these two scores is used to calculate the CT severity index for acute pancreatitis (table 2).[40] Patients with severe disease might recover but some die. Half of the early deaths occur within 14 days, whereas late deaths happen within 3 months, with multiple organ dysfunction originating first from the systemic inflammatory response and then from infection within pancreatic necrosis.

Early diagnosis of severe disease is important because it prompts an aggressive treatment, whereas mild

	0	1	2	3	4
Respiration					
PaO_2/FIO_2 (mm Hg)	>400	≤400	≤300	≤200 with respiratory support	≤100 with respiratory support
Coagulation					
Platelets ($\times 10^3$ per μL)	>150	≤150	≤100	≤50	≤20
Liver					
Bilirubin (μmol/L)	<20	20–32	33–101	102–204	>204
Cardiovascular					
Hypotension	No hypotension	MAP <70 mm Hg	Dopamine ≤5 or dobutamine (any dose)*	Dopamine >5 or epi ≤0·1* or norepi ≤0·1*	Dopamine >15 or epi >0·1*or norepi >0·1*
Central nervous system					
Glasgow coma score	15	13–14	10–12	6–9	<6
Kidney					
Creatinine (μmol/L) or urine output	<110	110–170	171–299	300–440 or <500 mL/day	>440 or <200 mL/day

MAP=mean arterial pressure. Epi=epinephrine. Norepi=norepinephrine. *Adrenergic agents administered for at least 1 h (doses given in μg/kg per min).

Table 1: **Sequential organ failure assessment (SOFA) score in acute pancreatitis**

	Points
Unenhanced CT	
Normal pancreas	0
Pancreatic enlargement	1
Pancreatic and peripancreatic changes	2
Single fluid collection	3
Two or more fluid collections	4
Contrast-enhanced CT	
Necrosis (proportion of cells)	
0%	0
<30%	2
30–50%	4
>50%	6
Score ≥7 predicts high morbidity and mortality	Score (0–10)

Table 2: **CT severity index**

attacks might be expected in the absence of severity. Several scoring systems have been used to help to identify patients at risk for adverse outcome, such as the Ranson criteria,[41,42] acute physiology and chronic health evaluation (APACHE II),[43,44] and SOFA scores (table 1). These scores assess injury in extrapancreatic organs; the greater the number of organs injured, the greater the score. Large variation exists between these scores in the ability to predict severe diseases.[45,46] Moreover, these scores should be repeated during hospitalisation, because their modifications can predict the outcome. During the first week of admission, organ dysfunction usually resolves, whereas worsening of organ dysfunction is associated with high mortality rate.[47,48] Absence of haemoconcentration on admission excludes the occurrence of pancreatic necrosis in most patients.[49,50] Another important factor that can contribute to severity is obesity.[51] Early CT severity score correlates well with the occurrence of complications, sepsis, mortality rate, and need for admission to intensive care units.[52]

Besides markers included in severity scores, serum concentrations of additional mediators on admission, such as C-reactive protein (CRP), cytokines, phospholipase A2, antiproteases, and procalcitonin have been correlated with disease development.[25,53,54] Serum concentrations of the trypsinogen activation peptide (TAP) and anionic trypsinogen 2 might also predict severity.[55–58] In healthy individuals, trypsinogen is cleaved by a duodenal enterokinase into active trypsin and TAP, whereas during acute pancreatitis inappropriate activation of trypsinogen within acinar cells results in systemic release of TAP and trypsin. However, markers other than CRP are not used in routine clinical practice.

Causation

Many causes for acute pancreatitis exist, and in 75–85% of patients the cause is easily identified. In developed countries, obstruction of the common bile duct by stones (38%) and alcohol abuse (36%) are the most frequent causes of acute pancreatitis (figure 1 and panel).[60]

***Panel:* Causes of acute pancreatitis**

Obstructive—biliary stone or sludge, pancreatic or ampullary tumour, choledochal cyst and choledochocele, annular pancreas, pancreas divisum (?), chronic pancreatitis, sphincter of Oddi dysfunction, duodenal obstruction (duodenal diverticulum, Crohn's disease)

Toxic—alcohol, scorpion bite, organophosphate insecticide

Class I drugs*—asparaginase, pentamidine, azathioprine, steroids,cytarabine, sulfamethoxazole-trimethoprim, didanosine, furosemide, sulfasalazine, mesalazine, sulindac, mercaptopurine, tetracycline, opiates, valproic acid, pentavalent antimonials, various oestrogens

Class II drugs*—paracetamol, hydrochlorothiazide, carbamazepine, interferon, cisplatin, lamivudine, cyclopenthiazide, octreotide, enalapril, phenformin, erythromycin, rifampicin

Postsurgery—ERCP, abdominal or cardiac surgery

Genetic—*PRSS1*, *SPINK1*, *CFTR*

Bacterial infection—Mycoplasma, legionella, leptospira, salmonella

Viral infection—Mumps, coxsackie, hepatitis B, cytomegalovirus, varicella-zoster, herpes

Parasitic infection—ascaris, cryptosporidium, toxoplasma

Metabolic—hypercalcaemia, hyperlipidaemia

Autoimmune—systemic lupus erythematosus, Sjögren's syndrome

Other—pregnancy, ischaemia, trauma

Idiopathic

*Drugs associated with pancreatitis in: 20 or more case reports and one positive re-exposure (class I); more than 10 and less than 20 case reports with or without re-exposure (class II); 10 or less case reports (class III).[59]

Gallstone-induced pancreatitis is caused by duct obstruction of gallstone migration. Obstruction is localised in the bile duct, the pancreatic duct, or both. Duct obstruction promotes pancreatitis by increasing ductal pressure with subsequent unregulated activation of digestive enzymes. Gallstones that can migrate in the bile duct and trigger acute pancreatitis are those with a diameter up to 5 mm. Most gallstones that have a diameter of 8 mm or more remain in the gallbladder.[61,62] Gallstone migration as a cause of pancreatitis can be suspected when patients have a previous history of biliary colic. Increase in serum hepatic enzyme concentrations (alanine aminotransferase concentration is three times or more the normal upper limit) on admission might help to predict biliary origin of pancreatitis (figure 3).[57] However, almost 15–20% of patients with biliary acute

pancreatitis have normal serum concentrations of hepatic enzymes.[63] Besides percutaneous ultrasound and CT, MRI is important for detection of gallstones. However, if suspicion of gallstone pancreatitis remains high despite a normal percutaneous ultrasonography or CT scan, endoscopic ultrasonography should be done whenever possible, because the bile duct is best imaged by this technique (figure 4).

Alcohol abuse is the second most frequent cause of acute pancreatitis, but the correlation between alcohol and pancreatitis is not completely understood. In experimental models, Gorelick[64] showed that ethanol directly sensitises acinar cells to cholecystokinin stimulation (figure 1). Acute pancreatitis develops in 10% of chronic alcohol abusers (>80 g daily intake). The development of pancreatitis is affected by both genetic and environmental factors.[65] Thus, failure to inhibit trypsin activity (gene mutation and absence of function of *SPINK1*) or failure to wash active trypsin into pancreatic ducts (gene mutation with dysfunction of the cystic fibrosis transmembrane conductance regulator gene, *CFTR*) might promote alcoholic pancreatitis.

Pancreas divisum is a common congenital anatomical variant of the pancreatic duct in about 7% of autopsy series. It results from the absence of fusion between the dorsal and ventral ductal systems.[66] The possible consequence of pancreas divisum is a stenosed or inadequately patent minor papilla, preventing normal drainage of pancreatic secretions and leading to increased intraductal pressure. However, whether pancreas divisum is related to pancreatitis is highly controversial.[67–69] Whether dysfunction of sphincter of Oddi can trigger acute pancreatitis by increasing intrapancreatic ductal pressure is another controversial issue.[70,71] Biliary sludge (figure 4) refers to a viscous bile suspension that contains cholesterol crystals and calcium bilirubinate granules embedded in strands of gallbladder mucus. Sludge is associated with bile stasis, long-lasting fast, distal bile duct obstruction, and total parenteral feeding. Most patients with biliary sludge are asymptomatic.[71,72] Biliary sludge is commonly seen in patients with recurrent acute pancreatitis of unknown origin, and cholecystectomy might prevent the recurrence of pancreatic disease.[73]

Intraductal papillary mucinous tumours might be another cause of acute pancreatitis. The tumour or mucus produced by the tumour obstruct the main pancreatic duct, a side branch of the main duct, or both types of duct.[74–77]

Freeman and colleagues[78] showed that 5·4% of 2347 patients were at risk of developing acute pancreatitis within 30 days after endoscopic retrograde cholangiopancreatography (ERCP). Moreover, asymptomatic hyperamylasaemia arises in 35–70% of patients after the procedure. The risk of acute pancreatitis is higher when the procedure is done to treat Oddi sphincter dysfunction than to remove gallstones in the bile duct.[79] Other risk factors for post-ERCP pancreatitis include young age, female sex, number of cannulation attempts of papilla before success, and poor emptying of pancreatic duct after opacification. Prevention of post-ERCP pancreatitis in high-risk patients might be achieved by placing a temporary pancreatic stent.[80,81]

Serum triglyceride concentrations greater than 11 mmol/L can worsen attacks of acute pancreatitis. However, hypertriglyceridaemia is a rare (1–4%) cause of acute pancreatitis, mostly seen in children with inherited disorders of lipoprotein metabolism (type I, II, and V hyperlipidaemia).[82,83] Most adults with hypertriglyceridaemia-related pancreatitis have a mild form of genetically inherited type I or type V disease, in addition to conditions that raise triglyceride

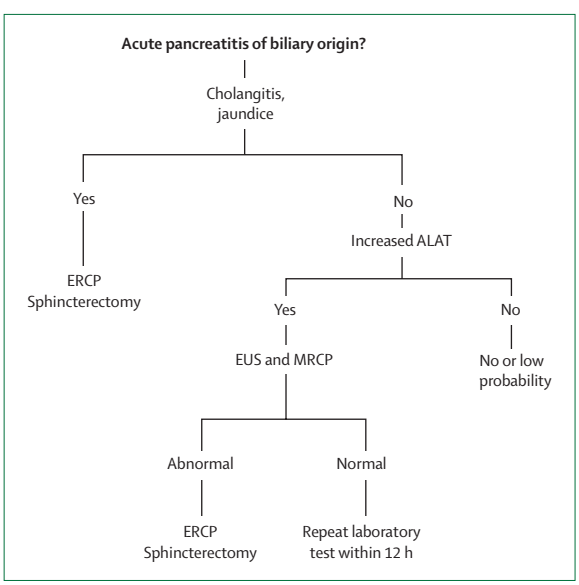

Figure 3: **Management of pancreatitis of biliary origin**
When patients have either jaundice or cholangitis, the biliary origin of disease is almost certain. Stones are preferentially removed by endoscopic retrograde cholangiopancreatography (ERCP) or during sphincterotomy. When diagnosis is unclear, endoscopic ultrasonography (EUS) and magnetic resonance cholangiopancreatography (MRCP) might help identify stones. ALAT=alanine aminotransferase.

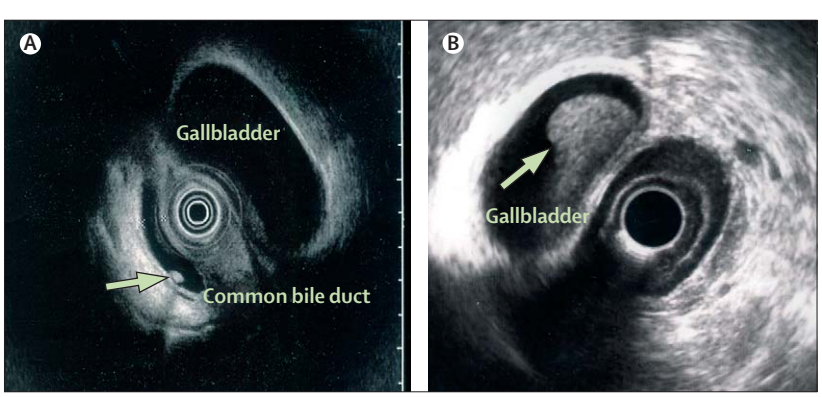

Figure 4: **Stones detection by endoscopic ultrasonography**
(A) A small stone undetectable by percutaneous ultrasonography is clearly seen by endoscopic ultrasonography (note the postacoustic shadow of the stone). (B) Well delineated sludge that sticks to the gallbladder wall (no postacoustic shadow).

concentrations such as obesity, diabetes mellitus, hypothyroidism, or pregnancy. Alcohol abuse and treatment by β blockers might also transiently increase serum triglyceride concentrations. The attacks of pancreatitis are usually mild, and more severe attacks can be successfully treated by plasmapheresis, especially in pregnant women.[84–86]

Hypercalcaemia is another rare and inconsistent cause of acute pancreatitis. Because the incidence of pancreatitis is low in patients with chronic hypercalcaemia, additional factors are probably needed to induce pancreatitis attacks.[87]

Drugs rarely induce acute pancreatitis (1·4–2%).[59,88] Most studies of drug-induced pancreatitis are case reports of few patients. A review classified 80 or more drugs that can induce pancreatitis into three categories, according to the number of reports and the existence of studies with drug re-exposure (panel). Class I drugs are those associated with 20 or more case reports with at least one drug re-exposure. Class II drugs are those described in more than 10 and less than 20 case reports with or without re-exposure. All other drugs associated with the disease belong to class III. Diuretics, anti-inflammatory agents, antibiotics, AIDS therapeutics, immunosuppressive agents, and cardiovascular drugs such as statins (class III) have all been implicated.[59,89] Drug-induced acute pancreatitis is either dose-dependent or dose-independent (hypersensitivity reaction), but most drug reactions are idiosyncratic.

Many infectious agents are associated with acute pancreatitis, but no microorganism has ever been identified within the pancreas. However, acute pancreatitis has been associated with viral or bacterial infections, and infestation with parasites (panel).[90] The pancreatic tropism of HIV is also well documented, with 4·7% in 939 HIV-positive patients being affected in one study.[91] Genetic mutations such as those in *CFTR* and *SPINK1* genes are frequent in HIV-positive patients with acute pancreatitis.[92] Pregnancy had long been regarded as a possible cause of acute pancreatitis, but recent studies emphasised the coexistence of additional factors such as gallstones or hyperlipidaemia to explain the higher frequency of the disease among pregnant women.[72,93] Acute pancreatitis is frequent after pancreatic or biliary surgery. Extradigestive procedures such as cardiopulmonary bypass for cardiac transplantation are also a risk factor; the longer the cardiopulmonary bypass and crossclamp times, the higher the risk.[94,95] Pancreatic ischaemia probably favours acute pancreatitis after surgery, shock, embolism, and systemic vasculitis.[96–98]

In most patients, acute pancreatitis is caused by gallstone obstruction or alcohol, and no genetic testing is needed. However, unexplained recurrent acute pancreatitis might be associated with known genetic mutations in the cationic trypsinogen gene protease serine 1 (*PRSS1*), *SPINK1*, or *CFTR*. Mutations in the *PRSS1* gene are seen in most patients with hereditary pancreatitis.[99,100] In the most frequent mutations, the function of trypsinogen is increased, causing premature enzyme activation and autolysis of acinar cells.

The pancreas synthesises SPINK1, a specific trypsin inhibitor, the function of which can be lost by mutation. Mutations are rarely associated with pancreatitis, but in association with other genetic traits, *SPINK1* mutations might favour pancreatic attacks in the presence of environmental triggers. In pancreatic ductal cells, CFTR controls chloride and bicarbonate fluxes (figure 1). Similar to *SPINK1* mutation, *CFTR* mutations alone are rarely associated with pancreatitis. However, genetic testing of *SPINK1* and *CFTR* mutations for pancreatitis might contribute to a better understanding of the mechanisms linking these mutations to the disease, in association with the environmental context and triggers.[101–103] Sarles and colleagues[104] described a patient with acute pancreatitis and hypergammmaglobulinaemia in 1965. Since then, autoimmune pancreatitis has been associated with Sjögren's syndrome, primary sclerosing cholangitis, and primary biliary cirrhosis. Autoimmune pancreatitis might disappear with steroid therapy.

In summary, the main causes of acute pancreatitis are gallstone migration and alcohol abuse. Other causes are uncommon, situational, or subject to continuous controversy, such as pancreas divisum or sphincter of Oddi dysfunction. Personal and familial history, clinical symptoms, laboratory tests, and percutaneous and endoscopic ultrasonography identify most of the causes, but 15–25% of episodes remain of unknown origin. How detailed the search for rare causes should be after the first episode of acute pancreatitis is debated. With new imaging techniques and genetic testing, the number of patients diagnosed with idiopathic pancreatitis should decrease.[105,106] However, the complexity of the pathophysiology of the disease, associated with genetic and environmental risks and acute triggers, preclude the identification of a unique cause for every episode of acute pancreatitis. Finally, besides specific treatment (mostly for gallstone-induced pancreatitis), the early therapeutic strategies are identical in all patients with acute pancreatitis.

Treatment

In mild forms of disease, besides the aetiological treatment (mostly for gallstone-induced pancreatitis), therapy is supportive and includes fluid resuscitation, pain relievers, oxygen administration, and antiemetics, whereas oral feeding is stopped (figure 5). By contrast, severe episodes (20% of patients) need management by a multidisciplinary team, including gastroenterologists, interventional radiologists, intensivists, and surgeons. However, despite efforts to start an appropriate treatment, mortality rate of severe attacks has not substantially changed during the past two decades. For these patients, resuscitation and close monitoring, nutritional support,

and management of pancreatic necrosis are important.[31,107] However, treatment of severe pancreatitis seems to differ considerably from centre to centre, according to local experience and guidelines.

An early medical treatment of acute pancreatitis is fluid resuscitation to correct fluid losses in the third space and maintain an adequate intravascular volume. Moreover, close monitoring of respiratory, cardiovascular, and renal function is needed to assess and treat complications associated with hypovolaemia. Oral feeding is stopped, whereas pain relievers, antiemetics, and oxygen administration can be helpful. Most episodes of acute pancreatitis are mild and self-limiting, needing only brief admission. Any patient with severe disease should be admitted to the intensive care unit, the criteria for admission being identical to those of other diseases.[108] Additionally, a stepdown unit must be considered in patients at high risk of deterioration, such as elderly patients, those who are obese, those needing a great volume of resuscitation, and those with pancreatic necrosis.[108]

To suppress the function of the exocrine pancreas, bowel rest by parenteral nutrition has been frequently advocated.[109] However, clinical and experimental studies showed that bowel rest is associated with intestinal mucosal atrophy and increased infectious complications due to bacterial translocation from the gut. Moreover, total parenteral nutrition is also associated with enhanced proinflammatory response. Thus, although mortality rate is not substantially different in patients treated with total parenteral nutrition or enteral nutrition, infections,[110,111] surgical interventions,[111] and non-infectious complications[111] are reduced by enteral nutrition. The type of enteral nutrition (gastric or jejunal) is debated. Although two studies showed that enteral nutrition can decrease the number of infections when the feeding tube is positioned in the jejunum,[31,112] Eatock and colleagues[113] showed no significant clinical difference between early nasogastric and nasojejunal feeding. Early enteral feeding should be provided, but the amount of calories and type of nutrient mixtures that should be given has yet to be established.[31]

Infection of pancreatic necrosis is a very important issue. This complication develops during the second or third week in 40–70% of patients. Because pancreatic infection is the leading cause of morbidity and mortality, early prevention of infected necrosis has been advocated. However, the benefit of antibiotic prophylaxis is highly debated; some studies and a meta-analysis showed that antibiotic prophylaxis reduced mortality and morbidity of pancreatic necrosis,[110,114–118] whereas another investigation did not show any advantage.[119] When infection is suspected and fine-needle aspiration of the pancreas for bacteriology done, the accepted treatment is to start antibiotics, intravenous imipenem or meropenem, for 14 days.[110] Such treatment is rapidly stopped if infection is not confirmed. Patients who develop pancreatic necrosis might need debridement and percutaneous or endoscopic drainage of fluid collections, pseudocysts, and abscesses.[120] However, such interventions are needed only when the pancreatic or peripancreatic tissues are infected, because debridement or drainage increase the risk to infect sterile tissues. When necrosis is sterile, mortality is low and necrosis is treated by a conservative approach, although surgery might be needed for late complications or persistent severe pancreatitis.

To discriminate between sterile and infected pancreatic necrosis when patients deteriorate, ultrasound- or CT-guided fine-needle aspirations of pancreatic tissues are repeatedly done.[107,120] When infection is proven or in the presence of abscesses, besides antibiotherapy,

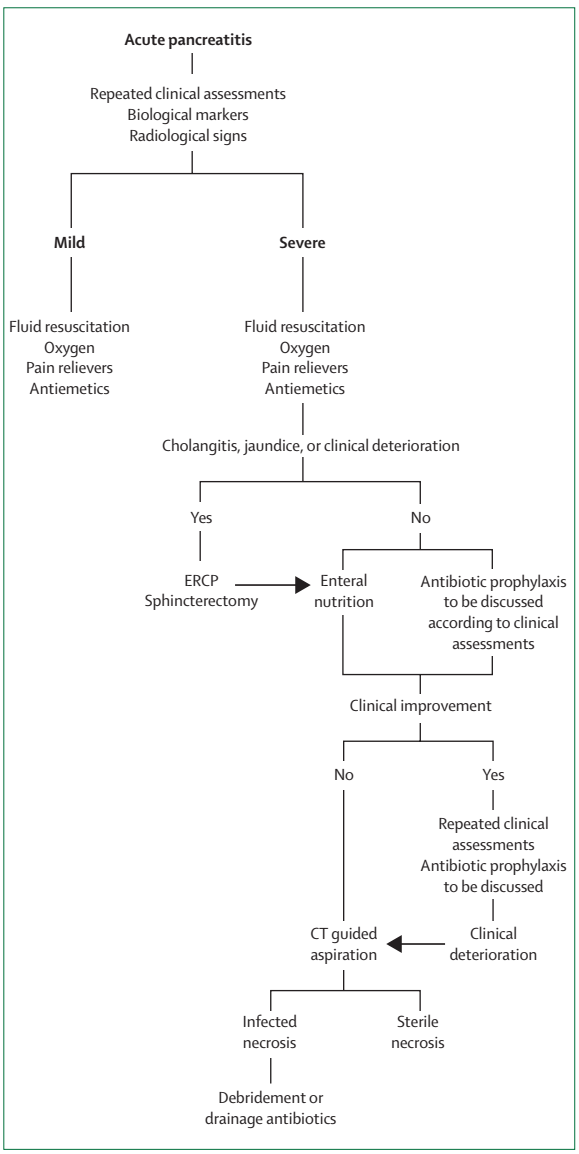

Figure 5: **Severity assessment and proposed therapeutic management for acute pancreatitis**

removal of infected tissues is done either by serial laparotomies before final abdomen closure or by a single laparotomy followed by subsequent closed drainages to remove residual necrosis. To keep the consequences of serial laparotomies to a minimum in critically ill patients and to decrease the ensuing increased mortality, several minimally invasive techniques are done. These procedures for debridement of infected necrosis include CT-guided and ultrasonography-guided percutaneous drainages, transgastric or transdudodenal endoscopic drainages, or minimally invasive laparoscopy with retroperitoneal access.[121,122] However, these techniques are still being developed and are indicated only in some patients.[120] Finally, abdominal decompression through midline laparotomy for abdominal compartment syndrome is another surgical procedure for severe acute pancreatitis.[123] Pancreatic and retroperitoneal inflammation associated with aggressive fluid administration increase the intra-abdominal pressure, decreasing abdominal organ perfusion with subsequent persistent organ dysfunction. The consequences of surgical decompression on the outcome remain unclear.

To keep pancreatic injury to a minimum, broad-spectrum antiprotease drugs such as aprotinin and gabexate mesilate have been advocated. Studies to test the efficacy of blockers of specific biochemical pathways that are activated during severe disease, including antagonists of platelet activating factor or inhibitors of basal and stimulated exocrine pancreatic secretion, have been disappointing and these treatments are not recommended.[110]

Most patients with gallstone-induced pancreatitis present with mild disease and quickly recover after early resuscitation. In patients with severe biliary pancreatitis, early (within 72 h) endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy have been recommended.[124,125] Such early procedures decrease the number of complications, such as biliary sepsis.[124,125] However, Folsch and colleagues[126] showed that early endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy are not beneficial in patients with biliary pancreatitis in the absence of biliary sepsis or obstruction. At present, the most accepted practice is to do endoscopic sphincterotomy if biliary obstruction, biliary sepsis, and persistent organ dysfunction are present.

The need for follow-up cholecystectomy to prevent recurrent episodes is also an important question. When stones are present in the gallbladder, laparoscopic cholecystectomy is done either during the same admission, when acute pancreatitis is mild, or delayed until resolution of the inflammatory response and clinical improvement (within 6 weeks). Delayed cholecystectomy is also indicated after endoscopic sphincterotomy, except when patients are too sick to undergo surgery.[110]

Conflict of interest statement

We declare that we have no conflict of interest.

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