Acute pancreatitis

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Search strategy and selection criteria

We searched PubMed for the term "acute pancreatitis", together with "aetiology", "pathogenesis", "prognostic parameters", "complications", "death", "treatment", or "prognosis". We included articles in English, French, German, and Spanish from Jan 1, 2009 to Dec 31, 2013, together with highly cited older publications that seemed necessary for full understanding. Moreover, we included several sets of guidelines, two of which cover almost the whole range of acute pancreatitis—namely, those from the American College of Gastroenterology [1] and the International Association of Pancreatology and American Pancreatic Association [2].

In this Seminar, we provide a comprehensive and balanced account of the advances since the 2008 Seminar in *The Lancet* on acute pancreatitis [3], highlight areas of controversy or international differences in practice, and describe concepts underlying the disease. The annual incidence of acute pancreatitis ranges from 13 to 45 per 100 000 people (appendix) [4]. In patients treated in hospital in the USA in 2009, acute pancreatitis was the most frequent principal discharge diagnosis in gastrointestinal disease and hepatology [5]. The number of discharges with acute pancreatitis as principal diagnosis was 30% higher than in 2000. Acute pancreatitis was the second highest cause of total hospital stays, the largest contributor to aggregate costs, and the fifth leading cause of in-hospital deaths, showing the importance of accurate data for the disorder.

Causes

Gallstones and alcohol misuse are the main risk factors for acute pancreatitis (appendix). During 20-30 years, however, the risk of biliary pancreatitis is unlikely to be more than 2% in patients with asymptomatic gallstones [6] and that of alcoholic pancreatitis is unlikely to exceed 2-3% in heavy drinkers [7]. Other factors, possibly genetic, therefore probably play a part. Drugs represent an additional cause of acute pacreatitis [8] (panel 1 and appendix).

Smoking might increase the risk ofacute pancreatitis [9, 10, 11]. There is no association between smoking and biliary pancreatitis, but the risk of non-gallstone-related acute pancreatitis has been shown to more than double (relative risk 2-29, 95% CI 1-63-3-22) in present smokers with 20 or more pack-years compared with never-smokers. Notably, in heavy smokers with a consumption of 400 or more grams of alcohol per month, the risk increased by more than four times (4-12, 1-98-8-60). Smoking duration rather than intensity increased the risk. It was beneficial to stop smoking, but only after two decades was the risk similar to non-smokers. These findings [9] could show that smoking is an independent risk factor for acute pancreatitis, but residual confounding factors and missing alcohol intake data are limitations of the study.

In four large retrospective studies, type 2 diabetes increased the risk of acute pancreatitis by 1-86-2-89 times [12, 13, 14, 15]. Compared with non-diabetics, the risk was particularly high in younger patients with diabetes (incidence rate ratio 5-26 in those younger than 45 years [95% CI 4-31-6-42]; 2-44 in those 45 years and older [2-23-2-66]) [15], and the excess risk was reduced by antidiabetic drugs [14]. The possibility of incretin-based therapies leading to acute pancreatitis is being debated [16, 17]. Whether failure of fusion of the dorsal and ventral pancreatic buds during gestation has any clinical or pathological results is unknown. In a group of patients with acute and

chronic pancreatitis, the prevalence of pancreas divisum was similar in those with and without idiopathic (7-5%) and alcoholic (7%) pancreatitis, showing that pancreas divisum alone does not cause the disease [18]. However, associations between pancreas divisum and mutations ofcystic fibrosis transmembrane conductance regulator *(CFTR)* of 47%, serine protease inhibitor Kazal-type 1 of 16%, or protease, serine 1 of 16%, were noted, suggesting a cumulative effect. This conclusion is not straightforward, however, because associations do not necessarily mean causation. Patients with pancreas divisum and *CFTR* mutations should be referred for genetic counselling, and endoscopic or surgical therapy should be withheld unless randomised studies show benefit [19].

Pancreatitis is the most frequent complication after endoscopic retrograde cholangiopancreatography (frequency 3-5% in unselected patients) [20]. It is mild or moderate in about 90% of cases. Independent patient-related and procedure-related risk factors for postendoscopic retrograde cholangiopancreatography pancreatitis act synergistically (table 1).

Panel 1: **Drugs for which a definite or probable association with acute pancreatitis has been reported (up to 2011)**

Definite

Acetaminophen, asparaginase, azathioprine, bortezomib, capecitabine, carbomazepine, Cimetidine, cisplatin, cytarabine, didanosine, enalapril, erythromycin, oestrogens, furosemide, hydrochlorothiazide, interferon alfa, itraconazole, lamivudine, mercaptopurine, mesalazine, olsalazine, methyldopa, metronidazole, octreotide, olanzapine, opiates, oxyphenbutazone, pentamidine, pentavalent antimony compounds, penformin, simvastatin, steroids, sulfasalazine, co-trimoxazole

Probable

Atorvastatine, carboplatin, docetaxel, ceftriaxon, cyclopenthiazide, didanosine, doxycycline, enalapril, famotidine, ifosfamide, imatinib, liraglutide, maprotiline, mesalazine, orlistat, oxaliplatine, rifampin, secnidazole, sitagliptine, sorafenib, tigecyclin, vildagliptine, sulindac, tamoxifen, tetracycline, valproate

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Table 1

Independent risk factors for PEP [20]

	Adjusted odds ratios (95% CI)	**Pooled incidence of PEP (patients with *vs* those without risk factor)**
Patient-related risk factors		
Definite risk factors		
Suspected sphincter of Oddi dysfunction	4-09 (3-37-4-96)	10-3% *vs* 3-9%
Female sex	2-23 (1-75-2-84)	4-0% *vs* 2-1%
Previous pancreatitis	2-46 (1-93-3-12)	6-7% *vs* 3-8%
Likely risk factors		
Younger age	1-09—2-87 (range 1-09—6-68)	6-1% *vs* 2-4%
Non-dilated extrahepatic bile ducts	Not reported	6-5% *vs* 6-7%
Absence of CP	1.87 (1.00-3-48)	4-0% *vs* 3-1%
Normal serum bilirubin	1-89 (1-22—2-93)	10-0% *vs* 4-2%
Procedure-related risk factors		
Definite risk factors		
Precut sphincterotomy	2-71 (2-02—3-63)	5-3% *vs* 3-1%
Pancreatic injection	2-2 (1-60—3-01)	3-3% *vs* 1-7%
Likely risk factors		
High number of cannulation attempts	2-40—3-41 (range 1-07—5-67)	3-7% *vs* 2-3%
Pancreatic sphincterotomy	3-07 (1-64—5-75)	2-6% *vs* 2-3%
Biliary balloon sphincter dilation	4-51 (1-51—13-46)	9-3% *vs* 1-9%
Failure to clear bile duct stones	3-35 (1-33—9-10)	1-7% *vs* 1-6%

PEP=postendoscopic retrograde cholangiopancreatography. CP=chronic pancreatitis.

Single-balloon or double-balloon enteroscopy can result in hyperamylasaemia and acute pancreatitis, probably because of repeated stretching of the small-bowel or mesenteric ligaments. The rates of hyperamylasaemia are reported to be 17% for double-balloon enteroscopy and 16% for single-balloon enteroscopy, but the rate of acute pancreatitis is much lower, at no more than 1% [21, 22]. Large prospective studies are needed to ascertain the true incidence of acute pancreatitis and potentially identify avoidable risk factors after double-balloon and single-balloon enteroscopy.

Pathogenesis Mechanisms of cellular injury

Pancreatic duct obstruction, irrespective ofthe mechanism, leads to upstream blockage of pancreatic secretion, which in turn impedes exocytosis of zymogen granules (containing digestive enzymes) from acinar cells. Consequently, the zymogen granules coalesce with intracellular lysosomes to form condensing or autophagic vacuoles containing an admixture of digestive and lysosomal enzymes. The lysosomal enzyme cathepsin B can activate the conversion of trypsinogen to trypsin. Findings from studies show lysosomal dysfunction in pancreatitis and an imbalance between the trypsinogen- activating isoform cathepsin B and the trypsin-degrading isoform cathepsin L [23]. The resulting accumulation of active trypsin within the vacuoles can activate a cascade of digestive enzymes leading to autodigestive injury (a concept first proposed by Hans Chiari [24]). A block in the healthy apical exocytosis of zymogen granules can cause basolateral exocytosis in the acinar cell, releasing active zymogens into the interstitial space (rather than the acinar lumen), with subsequent protease-induced injury to the cell membranes [25]. Evidence supporting a role for premature trypsinogen activation and autodigestion in acute pancreatitis comes from the discovery in patients with hereditary pancreatitis of a mutation in the trypsinogen gene, resulting in the formation of active trypsin that is resistant to degradation [26]. Genetically engineered mice with an absence of the trypsinogen 7 gene are protected from supramaximal caerulein-induced acinar injury, which supports this theory [26].

Acinar injury due to autodigestive processes stimulates an inflammatory response (infiltration of neutrophils and macrophages, and release of cytokines tumour necrosis factor a and interleukins 1, 6, and 8) within the pancreatic parenchyma. However, parenchymal inflammation has also been shown in trypsinogen-null mice after caerulein hyperstimulation [27], suggesting that inflammatory infiltration can occur independent of trypsinogen activation. Whatever the stimulus for inflammation, in a few cases the reaction is severe, with multiorgan failure and sepsis; sepsis is particularly thought to result from an increased propensity for bacterial translocation from the gut lumen to the circulation [28].

The toxic effects of bile acid itself on acinar cells have attracted attention as a possible pathogenetic factor in biliary pancreatitis. Bile acids can be taken up by acinar cells via bile acid transporters located at apical and basolateral plasma membranes [29] or by a G-protein-coupled receptor for bile acids (Gpbar1) [30]. Once within the cell, bile acids increase intra-acinar calcium concentrations via inhibition of sarcoendoplasmic Ca^{2+}-ATPase and activate signalling pathways, including MAPK and PI3K, and transcription factors such as NF-κB, thereby inducing synthesis of proinflammatory mediators [31]. However, whether these processes are clinically important remains unclear since clinical evidence for biliopancreatic reflux is scarce.

Alcoholic pancreatitis

Alcohol is known to exert direct toxic effects on the pancreas, but additional triggers or cofactors seem to be necessary to initiate overt pancreatitis. Early studies focused on the effects of alcohol on the sphincter of Oddi as a possible mechanism of duct obstruction leading to pancreatitis (similar to that for biliary pancreatitis). However, the results were controversial, with both decreased and increased sphincter of Oddi tone reported [32]. There is more consistent evidence that the effects of alcohol on small pancreatic ducts and the acinar cells themselves play a part in alcohol-induced pancreatic injury [32]. Alcohol increases the propensity for precipitation of pancreatic secretions and the formation of protein plugs within pancreatic ducts owing to changes of lithostathine and glycoprotein 2, two non-digestive enzyme components ofpancreatic juice with self-aggregation properties; and to increased viscosity of pancreatic secretions because of CFTR dysfunction [32, 33].

The protein plugs enlarge and form calculi, causing ulceration of adjacent ductal epithelium, scarring, further obstruction, and, eventually, acinar atrophy and fibrosis [33].

Experimental studies have shown that alcohol increases digestive and lysosomal enzyme content within acinar cells and destabilises the organelles that contain these enzymes [34], thereby increasing the potential for contact between digestive and lysosomal enzymes, and facilitating premature intracellular activation of digestive enzymes. These effects of alcohol on acinar cells are probably a result of the metabolism of alcohol within the cells, leading to the generation of toxic metabolites (acetaldehyde, fatty acid ethyl esters, and reactive oxygen species) and changes in the intracellular redox state (appendix, figure).

Alcohol exerts toxic effects on pancreatic stellate cells (resident cells of the pancreas that regulate healthy extracellular matrix turnover) [32]. PSCs are activated by alcohol, its metabolites, and oxidative stress to convert into a myofibroblast-like phenotype that synthesises cytokines, which can contribute to the inflammatory process during acute pancreatitis (figure).

Despite the known detrimental effects of alcohol and its metabolites on the pancreas, only a few drinkers develop overt disease, prompting a search for the additional insult needed for precipitating pancreatitis. Unfortunately, none of the candidate trigger factors investigated so far (diet, amount and type of alcohol consumed, pattern of alcohol consumption, presence of hyperlipidaemia, smoking, and inherited factors) have been shown to have a clear role. The role of smoking in alcoholic acute pancreatitis is particularly controversial [35, 36] because although animal studies have shown detrimental effects of cigarette smoke extract, nicotine, and nicotine-derived nitrosamine ketone on duct or acinar cells [37, 38, 39], the clinical relevance of these findings is mitigated by the very close association between heavy smoking and drinking, making it difficult to ascribe the initiation of acute pancreatitis in human beings to smoking alone. Nevertheless, there is general consensus that smoking accelerates the progression of alcoholic pancreatitis [40]. Bacterial endotoxinaemia is another possible trigger factor, as shown by experimental evidence that an endotoxin challenge in alcohol-fed rats leads to acute pancreatitis, whereas alcohol feeding alone causes no damage [41]. Since alcohol is known to increase gut permeability, an inability to detoxify circulating endotoxin could make some drinkers susceptible to overt disease.

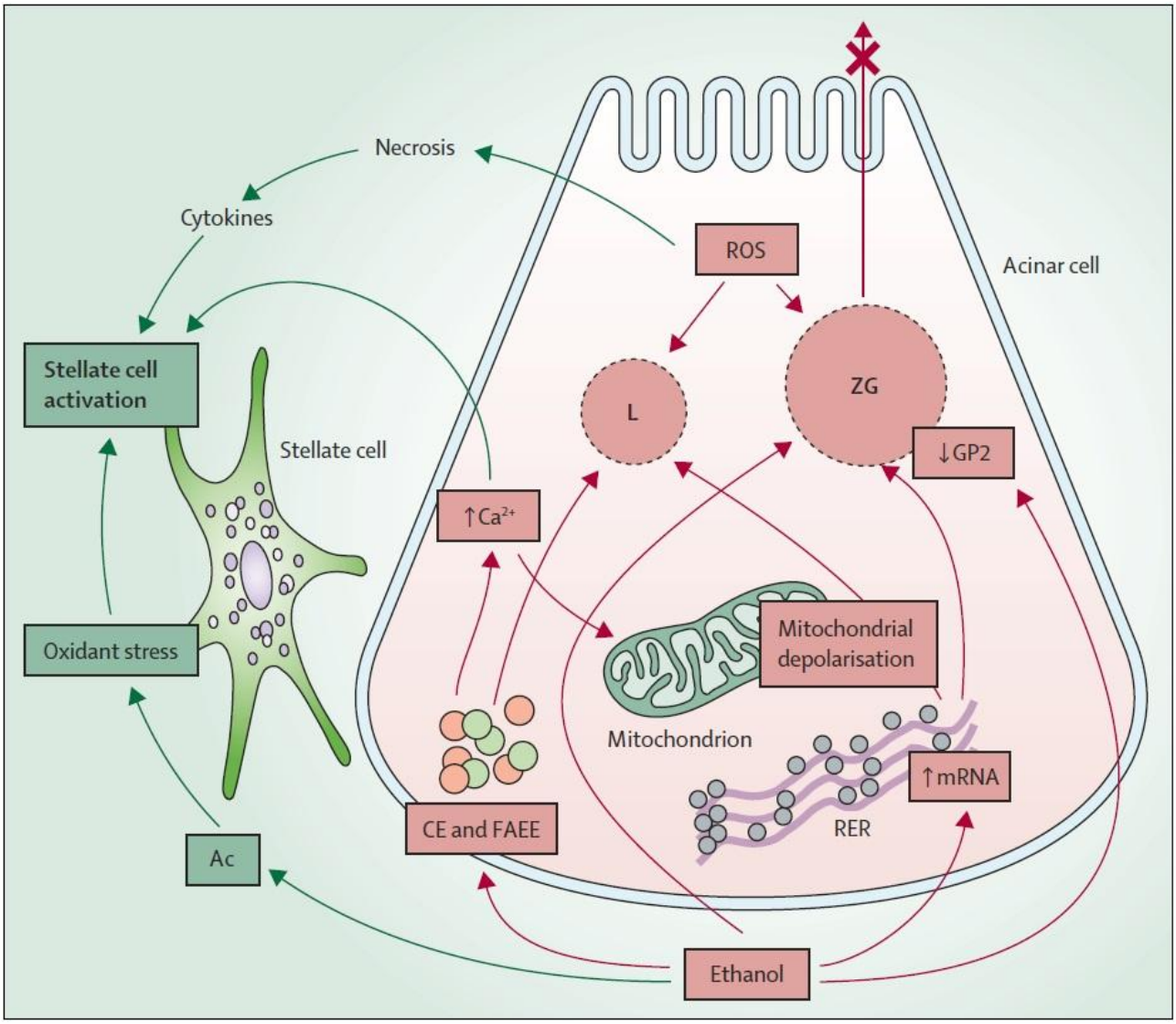

Fig. 1. Effects of alcohol on the pancreatic acinar and stellate cell, on the basis of experimental in-vitro and in-vivo evidence.

Pancreatic acinar cells metabolise alcohol via both oxidative and non-oxidative pathways, and exhibit changes that predispose the cells to autodigestive injury, necroinflammation, and cell death. These changes include: destabilisation of lysosomes and zymogen granules (mediated by oxidant stress [ROS, CE, FAEE, and decreased GP2, a major structural component of zymogen membranes); increased digestive and lysosomal enzyme content (because of increased synthesis [increased mRNA] and impaired secretion); increased activation of transcription factors (NF-κB and AP-1) that regulate cytokine expression; and a sustained increase in cytoplasmic Ca^{2+} and mitochondrial Ca^{2+} overload, leading to mitochondrial depolarisation. Pancreatic stellate cells have the capacity to oxidise alcohol to acetaldehyde, which is associated with the generation of reactive oxygen species, leading to oxidant stress. Pancreatic stellate cells are activated, on exposure to alcohol, to a myofibroblast-like phenotype, stimulating synthesis of proinflammatory mediators and cytokines by the cells. This sensitises the pancreas such that in the presence of an appropriate trigger or cofactor, overt injury is initiated. The effects of ethanol on acinar cells are represented by red arrows and on stellate cells by green arrows. Ca^{2+}=calcium. Ac=acetaldehyde. CE=cholesteryl esters. FAEE=fatty acid ethyl esters. GP2=glycoprotein 2. L=lysosomes. RER=rough endoplasmic reticulum. ROS=reactive oxygen species. ZG=zymogen granules. Reproduced with permission from reference 30.

Genetic factors related to digestive enzymes, trypsin inhibitors, cytokines, CFTR, MHC antigens, alcohol- metabolizing enzymes, oxidant stress-related proteins, and detoxifying enzymes have not shown an association with alcoholic pancreatitis. Investigators of a genome-wide

association study reported an association between overexpression of claudin 2 (a tight-junction protein) and increased risk of alcoholic pancreatitis, with the protein overexpressed on the basolateral membranes of acinar cells in these patients [42]. However, the functional significance of this finding remains unclear.

A final aspect of pathogenesis is the multitude of signalling pathways and molecules that are perturbed within the acinar cell upon exposure to injurious agents, but accumulating evidence points to aberrant intracellular calcium signalling as the final common mechanism for acinar injury (appendix) [43, 44].

Classification

The Atlanta classification [45] is the standard classification of the severity of acute pancreatitis. The recently published revised classification [46] provides definitions of the clinical and radiologic severity of acute pancreatitis. Clinical severity of acute pancreatitis is stratified into three categories: mild, moderately severe, and severe (table 2).

Patients with mild acute pancreatitis (no organ failure or systemic or local complications) usually do not need pancreatic imaging and are frequently discharged within 3-7 days of onset of illness.

Moderately severe acute pancreatitis is characterised by one or more of transient organ failure (defined as organ failure lasting <48 h), systemic complications, or local complications. Organ failure includes respiratory, cardiovascular, and renal failure using the same criteria as in the Atlanta Symposium of 1992 [45]. The revised classification recommends that the modified Marshall scoring system should be used to characterise the severity of failure of these three systems. Systemic complications are defined as exacerbations of pre-existing comorbidities, including congestive heart failure, chronic liver disease, and chronic lung disease. Local complications include interstitial pancreatitis (peripancreatic fluid collections and pancreatic pseudocysts) and necrotising pancreatitis (acute necrotic collections and walled-off necrosis; panel 2). Patients who have moderately severe acute pancreatitis might need a longer stay in hospital and have a higher mortality than patients with mild acute pancreatitis.

Table 2

Definition of severity in acute pancreatitis

Atlanta classification 1992 [45]	**Revised Atlanta classification 2012 [46]**	**Determinant-based classification 2012 [47]**
Mild No organ failure and no local complications	No organ failure and no local or systemic complications	No (peri)pancreatic necrosis and organ failure
Moderately severe ..	Transient organ failure (<48 h) and/or local or systemic complications without persistent organ failure (>48 h)	Sterile (peri)pancreatic necrosis and/or transient organ failure (<48 h)
Severe Local complications and/or organ failure: PaO_2 <60% or creatinine >152-6 pmol/L or shock (systolic blood pressure <60 mm Hg) or gastrointestinal bleeding (>500 mL/24 h)	Persistent organ failure (>48 h):* single organ failure or multiple organ failure	Infected (peri)pancreatic necroses or persistent organ failure (>48 h)
Critical ..		Infected (peri)pancreatic necroses and persistent organ failure

Neither Atlanta classifications have a fourth critical group; this group is solely in the determinant-based classification.
*Persistent organ failure is now defined by a modified Marshall score (appendix) [48].

Severe acute pancreatitis is characterised by the presence of persistent single-organ or multiorgan failure (defined by organ failure that is present for >48 h). Most patients who have persistent organ failure have pancreatic necrosis and a mortality of at least 30%.

An alternative stratification of acute pancreatitis severity has been proposed, which includes four categories rather than three (table 2) [47]. These are mild (absence of necrosis or organ failure),

moderately severe (sterile necrosis and/ or transient organ failure), severe (infected necroses or persistent organ failure), and critical (infected necroses and persistent organ failure). Studies will be needed to ascertain whether it is more clinically relevant to stratify patients into these three or four categories of severity.

For radiological severity of acute pancreatitis, the revised classification provides detailed definitions of the imaging features of the disease. Acute peripancreatic fluid collections occur within the first several days of interstitial pancreatitis. They are homogeneous in appearance, usually remain sterile, and most often resolve spontaneously. An acute peripancreatic fluid collection that does not resolve can develop into a pseudocyst, which contains a well defined inflammatory wall. There is very little, if any, solid material within the fluid of a pseudocyst.

Of particular importance is the radiological definition of acute necrotic collections and walled-off necrosis. Previously, the site of acute necrotic collections in necrotising pancreatitis was thought to include the pancreatic parenchyma and peripancreatic tissue or, on rare occasions, only the pancreatic parenchyma. It is now recognised that acute necrotic collection can include only the peripancreatic tissue. Patients with peripancreatic necrosis have an increased morbidity and mortality compared with interstitial pancreatitis. Acute necrotic collections in necrotising pancreatitis can be sterile or infected. The natural history of acute necrotic collections is variable. They can become smaller and, on rare occasions, wholly disappear. Most often, acute necrotic collections develop a well defined inflammatory wall surrounding varying amounts of fluid and necrotic debris—termed walled-off necrosis—which can be either sterile or infected.

This revised classification needs to be tested to assess its clinical usefulness, and is likely to undergo further revisions in the future. The appendix lists clinical presentation and physical examination, and the essential abdominal and systemic complications of acute pancreatitis.

Panel 2: **Revised 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 peripancreatic necrosis.

Necrotising pancreatitis

Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis.

- CECT criteria
- Lack of pancreatic parenchymal enhancement by intravenous contrast agent.
- Presence of findings of peripancreatic necrosis.

Acute pancreatitis fluid collection

Peripancreatic fluid associated with interstitial oedematous pancreatitis with no associated peripancreatic necrosis. 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 inflammation wall, usually outside the pancreas, with little or no necrosis. Usually occurs more than 4 weeks after onset of interstitial oedematous pancreatitis.

Diagnosis

Main diagnostic procedures

Clinicians are interested in confirmation of the diagnosis and exclusion of differential diagnoses (appendix). In accordance with the revised Atlanta classification, acute pancreatitis can be diagnosed if at least two ofthe following three criteria are fulfilled: abdominal pain (acute onset of persistent and severe epigastric pain, often radiating to the back); serum lipase (or amylase) activity at least three-times the upper limit of normal; or characteristic findings of acute pancreatitis on contrast-enhanced CT or, less often, MRI or transabdominal ultrasonography [46]. Diagnostic imaging is essential in patients with a slight enzyme elevation (appendix). Importantly, pancreatic enzyme concentrations on admission are not associated with disease severity [49]. The disease can be serious, even fatal, although the enzymes are only slightly increased (<three-times normal).

- CECT criteria
  - Well circumscribed; usually round or oval.
  - Homogeneous fluid density.
  - No non-liquid component.
  - Well defined wall that is wholly encapsulated.
  - Maturation usually needs >4 weeks after onset of acute pancreatitis; occurs after interstitial oedematous pancreatitis.

Acute necrotic collection

A collection containing variable amounts of both fluid and necrosis associated with necrotising pancreatitis; the necrosis can include the pancreatic parenchyma and/or the peripancreatic tissue.

- CECT criteria
  - Occurs only in the setting of acute necrotising pancreatitis.
  - Heterogeneous and non-liquid density of varying degrees in different locations (some seem homogeneous early in their course).
  - No definable wall encapsulating the collection
  - Intrapancreatic and/or extrapancreatic.

Walled-off necrosis

A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well defined inflammatory wall. Usually occurs >4 weeks after onset of necrotising pancreatitis.

- CECT criteria
  - Heterogeneous with liquid and non-liquid density, with varying locations (some can seem homogeneous)
  - Well-defined wall that is wholly encapsulated.
  - Intrapancreatic and/or extrapancreatic.
  - Maturation usually needs 4 weeks after onset of acute necrotising pancreatitis.

CECT=contrast-enhanced CT. Reproduced with permission from reference 46.

Laboratory tests

In addition to serum amylase and lipase, the following variables should be established on admission: complete blood count without differential; concentrations of electrolytes, blood urea nitrogen (BUN), creatinine, serum glutamic pyruvic transaminase, serum glutamic oxalic transaminase, alkaline phosphatase, and blood sugar; coagulation status; and total albumin. Arterial blood gas analysis is generally indicated whenever oxygen saturation is less than 95% or the patient is tachypnoeic. The frequency of repeat determinations depends on the clinical course.

ECG and chest radiograph

50% or fewer cases of ST segment elevations and negativities are registered, mainly in the posterior wall, without myocardial infarction. Chest radiographs in two planes can show pleural effusions and pulmonary infiltrates, which are signs of severe disease. Abdominal panoramic radiographs (upright or left lateral position) can be used for diagnosis too. Ileus is shown by a sentinel loop (isolated bowel loop in left-upper or middle abdomen) or colon cutoff sign (absence of air in left

colonic flexure or descending colon). Pancreatic calcifications represent proof of chronic pancreatitis—ie, that the patient is having an episode of acute superimposed on chronic pancreatitis, rather than a first episode of acute pancreatitis.

CT

Unenhanced CT scoring systems assess the extent of pancreatic and peripancreatic inflammatory changes (Balthazar score [50] or pancreatic size index [51]), or both peripancreatic inflammatory changes and extrapancreatic complications (mesenteric oedema and peritoneal fluid score [52], extrapancreatic score [53], or extrapancreatic inflammation on CT score [54]).

Two CT scoring systems need intravenous contrast agents to establish the presence and extent of pancreatic parenchymal necrosis. The CT severity index [55] combines quantification of extrapancreatic inflammation with extent of pancreatic necrosis, whereas the modified CT severity index [56] assigns points for extrapancreatic (eg, vascular, gastrointestinal, or extrapancreatic parenchymal) complications and presence of pleural effusions or ascites.

Contrast-enhanced CT is the gold standard for diagnostic imaging to help to establish disease severity (the appendix contains axial contrast-enhanced CT scans of the pancreas of a patient with acute pancreatitis on admission and 1, 10, and 20 days later). However, the predictive accuracy of CT scoring systems for severity of acute pancreatitis is similar to clinical scoring systems. A CT scan on admission solely for severity assessment in acute pancreatitis is therefore not recommended [57]. An early CT scan—ie, done within the first 4 full days after symptom onset (days 0-4)—does not show an alternative diagnosis, help with the distinction of interstitial versus necrotising pancreatitis, or provide evidence of an important complication [58]. An early CT scan should therefore be obtained only when there is clinical doubt about the diagnosis of acute pancreatitis, and other life-threatening disorders have to be excluded.

Prognostic variables

Existing scoring systems (appendix) seem to have reached their maximum effectiveness in the prediction of persistent organ failure in acute pancreatitis. Sophisticated combinations of predictive rules are more accurate, but cumbersome, and therefore of restricted clinical use, and new approaches are needed [59].

One such approach is the harmless acute pancreatitis score (HAPS), which enables identification of mild cases of acute pancreatitis (which is most of them) within 30 min of inpatient admission, even by non-specialists. Two prospective studies [60], one monocentric and the other multicentric, showed that mild acute pancreatitis can be predicted with 98% accuracy in patients with no rebound tenderness or guarding and normal haematocrit and serum creatinine concentrations. Studies from Sweden [61] and India [62] support the accuracy of HAPS. This score thus identifies most patients who have neither developed, or will develop, necrotising pancreatitis or organ failure, and will therefore not need intensive care. HAPS can be used in the community care setting, in which the treating physician can triage the patients who need early transfer to more specialised centres for more aggressive management and meticulous monitoring [62]. The score might even be able to establish whether the patient could be cared for adequately and more economically as an outpatient.

Therapy

The patient's management begins on the emergency ward, where acute pancreatitis has to be confirmed, the risk stratified, and basic treatment initiated. This treatment includes early fluid resuscitation, analgesia, and nutritional support (appendix). Patients undergoing volume resuscitation should have the head of the bed raised, undergo continuous pulse oximetry, and receive supplemental oxygen. Supplemental oxygen has been shown to more than half mortality in patients older than 60 years [63].

In experimental pancreatitis in the rat, pancreatic microvascular perfusion is reduced, which is aggravated by arterial hypotension [64]. The situation in human beings, however, remains unclear. Neither comparisons of aggressive versus non-aggressive resuscitation protocols (4 L *vs* 3-5 L within the first 24 h) nor goal-directed fluid therapy (goals have included BUN concentration, central venous pressure, haematocrit concentration, heart rate, blood pressure, and urine output) have yielded clear results [65]. The investigators of one retrospective study showed that early fluid resuscitation

was associated with reduced incidence of systemic inflammatory response syndrome and organ failure at 72 h [66], but too little fluid is just as deleterious as too much. In one study, rapid haemodilution increased both the incidence of sepsis within 28 days and in-hospital mortality [67]. In another, the administration of a small amount of fluid was not associated with a poor outcome, but the need for a large amount of fluid was [68].

With regard to what should be infused, the recommendations of the American College of Gastroenterology (ACG) and International Association of Pancreatology (IAP)/American Pancreatic Association (APA) guidelines are very similar: ACG suggests that lactated Ringer's solution might be preferred to isotonic crystalloid replacement fluid [1], whereas IAP/APA merely state [2] that Ringer's lactate should not be given to the few patients with hypercalcaemia for initial fluid resuscitation. The two sets of guidelines differ with regard to rate of infusion, with ACG suggesting a rate of 250-500 mL/h and IAP/APA suggesting 5-10 mL/kg per h. If the ACG recommendation is assumed to be for a patient weighing 70 kg, following the IAP/APA guideline would lead to a much higher rate of infusion, of 50-700 mL/h. Only ACG makes a firm recommendation as to when infusion should begin, stating that early aggressive intravenous hydration is most beneficial in the first 12-24 h and could have little benefit beyond this time [1].

These recommendations are essentially based on a prospective multicentre randomised study [69] in which resuscitation with lactated Ringer's solution reduced by 84% during the first 24 h compared with normal saline. Infusion started with a bolus of 20 mL/kg bodyweight followed by 3 mL/kg for 8-12 h. Crucial, however, is adjustment of the infusion rate depending on the results of measurements of intervals of no more than 6 h for at least 24-48 h. One decisive variable is BUN because investigators have shown that increased BUN concentration at admission and during the first 24 h are independent risk factors for mortality in acute pancreatitis [70, 71]. The recommendation has been made to adjust fluid resuscitation during the first 24 h on the basis of whether BUN concentration increases or decreases [72].

Pain treatment has absolute priority on admission. Unfortunately, findings from a systematic review showed that the randomised controlled trials (RCTs) comparing different analgesics were of low quality and did not clearly favour any particular analgesic for pain relief [73]. Until a conclusive study is reported, the prevailing guidelines for acute pain management in the perioperative setting should be followed [74].

Patients in high-volume centres (>118 admissions per year) have a 25% lower relative risk of death than do those in low-volume centres [75]. Patients who do not respond to early resuscitation or display persisting organ failure or widespread local complications should therefore be transferred to a pancreatitis centre (if available) with multidisciplinary expertise, including therapeutic endoscopy, interventional radiology, and surgery. Patients with persistent systemic inflammatory response syndrome, increased concentrations of BUN or creatinine, increased haematocrit, or underlying cardiac or pulmonary illness, should be admitted for monitoring—either intensive or intermediate care, depending on availability. All other patients, especially those in whom HAPS [60] predicts harmless acute pancreatitis, can be treated on a general ward.

In mild acute pancreatitis, oral feedings can be started if there is no nausea and vomiting, and abdominal pain has resolved [1]. Findings from a systematic review of 15 RCTs [76] showed that either enteral or parenteral nutrition is associated with a lower risk of death than no supplementary nutrition. Enteral nutrition was associated with a lower risk of complications than parenteral nutrition, but not with a significant change in mortality. However, timing is crucial. The investigators of a systematic review of 11 RCTs showed that when started within 48 h of admission, but not later, enteral nutrition, compared with parenteral nutrition, significantly reduces the risk of multiorgan failure, pancreatic infectious complications, and mortality [77]. Many studies have proposed that enteral nutrition should be given via a nasoduodenal rather than nasojejunal tube, but a firm recommendation cannot yet be given [78, 89, 90, 91]. An initial attempt at nasoduodenal intubation seems advisable, but the pancreatic head inflammation in severe acute pancreatitis can cause duodenal stenosis, necessitating endoscopic placement. Nausea and vomiting because of persisting gastroparesis, ileus, or postprandial pain suggests parenteral nutrition via a central venous catheter.

Glutamine supplementation has been discussed for patients with critical acute pancreatitis leading to catabolism. Findings from a meta-analysis of 12 RCTs [82] showed that glutamine supplementation significantly reduced the risk of mortality and total infectious complications in parenterally—but not enterally—fed patients, but did not shorten the hospital stay. The absence of a positive effect of enteral glutamine supplementation was attributed to the fact that glutamine is largely metabolised in the gut and liver so that the plasma glutamine concentration is lower after enteral than after intravenous administration. An additional point to note is that treatment with antioxidants is ineffective [83, 84, 85].

A Cochrane review [86] showed no evidence that routine early endoscopic retrograde cholangiopancreatography significantly affects mortality and local or systemic complications in patients with acute gallstone pancreatitis, irrespective of predicted severity. The results, however, support present recommendations [86] that early endoscopic retrograde cholangiopancreatography should be considered in patients with coexisting cholangitis or biliary obstruction.

Management of local complications Necrosis

Prophylactic antibiotics are not indicated [87, 88, 89, 90]. Surgical resection of pancreatic necroses can be achieved by open, laparoscopic, or staged necrosectomy (open-staged or closed-continuous lavage). These methods do not compete with, but rather complement, other techniques. No guidelines exist, but there is consensus that surgical intervention should be done—if at all—at a late stage, at least 2 weeks after the onset of pancreatitis [91].

More conservative interventions than surgery now predominate [92, 93] as a result of two pioneering advances. Antibiotic treatment alone can heal infected necrosis [94]. This is now the first step when such lesions are shown. Antibiotic treatment is possible in almost two-thirds of patients with necrotising pancreatitis, with a mortality of 7% [95]. Seifert and colleagues [96] successfully introduced debridement of infected necrosis after fenestration of the gastric wall. This form of intervention has become widely used and other routes of access have been developed, but it should be restricted to specialist centres. Long-term success can then be achieved in two-thirds of patients [97]. Endoscopic transgastric necrosectomy compares favourably with surgery [98]. Clinical trials are needed to validate the various options for intervention.

Van Santvoort and colleagues [99] compared step-up management of infected necrosis (placement of percutaneous catheters in addition to treatment with antibiotics, if necessary followed by minimally invasive necrosectomy) with open necrosectomy. This step-up approach reduced new-onset multiorgan failure by 29%. However, the study was underpowered to detect a difference in mortality.

In patients with walled-off necrosis, physicians should intervene only in the event of symptoms attributable to the collection (persistent abdominal pain, anorexia, nausea, or vomiting from mechanical obstruction or secondary infection) [72]. In this case, direct endoscopic necrosectomy is possible in skilled hands [100].

Pseudocyst

Prognostic factors for the development of pseudocysts are alcohol misuse and initially severe disease. Spontaneous resolution occurs in a third of patients with a pseudocyst. Prognostic factors for this resolution are no or mild symptoms, and a pseudocyst diameter of no more than 4 cm [101]. Symptomatic pseudocysts can be successfully decompressed by endoscopic cystogastrostomy with endoscopic ultrasound guidance [102].

Ductal disruption

Ductal disruption can result in unilateral pleural effusion, pancreatic ascites, or enlarging fluid collection. If the disruption is focal, placement of a bridging stent via endoscopic retrograde cholangiopancreatography usually promotes duct healing [103]. When ductal disruption occurs in an area of widespread necrosis, optimum management needs a multidisciplinary team oftherapeutic endoscopists, interventional radiologists, and surgeons [104].

Peripancreatic vascular complications

Splenic vein thrombosis has been reported in up to 20% of patients with acute pancreatitis undergoing imaging [105]. The risk of bleeding from gastric varices is less than 5%, and splenectomy

is not recommended. Pseudoaneurysms are rare, but cause serious complications in 4-10% of cases [106]. Mesenteric angiography with transcatheter arterial embolisation is the first-line treatment [107].

Management of extrapancreatic complications

Extrapancreatic infections, such as bloodstream infections, pneumonia, and urinary tract infections, occur early in up to 24% of patients with acute pancreatitis, and can double mortality [108, 109]. If sepsis is suspected, it is reasonable to start antibiotics while waiting for blood culture results. If culture results are negative, antibiotics should be discontinued to reduce the risk of fungaemia [110] or *Clostridium difficile* infection [72].

Aftercare Refeeding

Basic treatment of acute pancreatitis should be continued until the patient shows distinct clinical improvement (freedom from pain and normal body temperature and abdominal findings). No binding recommendation for severe acute pancreatitis exists; the decision is taken on an individual basis. In mild acute pancreatitis, oral feeding should be resumed as soon as possible according to the present European Society for Parenteral and Enteral Nutrition guidelines [111]. When and how this feeding should be resumed remains undefined. The beginning of refeeding certainly does not depend on the normalisation of lipase [112]. The decision should perhaps be left to the patients—ie, they can eat when they are hungry [112, 113]. Positive experience with refeeding at the patient's request has been reported with widely varying diets: unspecified [114], soft diet [115], and full diet with [116] or without [117] fat restriction. Unfortunately, however, oral refeeding can lead to pain relapse and therefore to a longer hospital stay (appendix).

Imaging procedures

Patients with acute pancreatitis of unknown origin should undergo endosonography to exclude stones or sludge in the gallbladder or bile ducts. Endosonography or magnetic resonance cholangiopancreatography can be indicated to exclude a tumour. Tumour-related acute pancreatitis can seem to heal before flaring up again [118].

Transient exocrine and endocrine pancreatic insufficiency

Both exocrine and endocrine transient pancreatic insufficiency can occur during healing [119, 120, 121]. Pancreatic function should therefore be monitored, which is generally normal again 3 months after abatement of acute pancreatitis. Pancreatic enzyme substitution is not usually necessary, but can be temporarily necessary after a severe attack.

Endocrine pancreatic function should be checked after about 3 months (by fasting and postprandial blood sugar concentrations, possibly by HbA_{1C} measurement). Severe acute pancreatitis is often followed by diabetes mellitus [122].

Transition to chronic pancreatitis

In a German study [123], over a period of almost 8 years, only alcoholics developed chronic pancreatitis, independently of both severity of first acute pancreatitis and discontinuation of alcohol and nicotine. The cumulative risk of the development of chronic pancreatitis was 13% within 10 years and 16% within 20 years. The risk of chronic pancreatitis in those who survived the second episode of acute pancreatitis was 38% within 2 years. Nicotine misuse increased the risk substantially. Similar investigations from Denmark [124] and the USA [125] showed a transition to chronic from acute pancreatitis in 24-1% of patients after 3-5 years and 32-3% after 3-4 years, respectively. In both studies, transition also occurred occasionally in patients with non-alcohol-induced pancreatitis.

Ductal scarring can be seen on endoscopic retrograde cholangiopancreatography, even after healing, but should, under no circumstances, lead to diagnosis of chronic pancreatitis and substitution of pancreatic enzymes [126].

Prevention

One study [127] showed that interventions by medical personnel (structured talks with patients by nurses trained to inform patients how and why they should stay abstinent) at 6-month intervals significantly lowered the recurrence rate of alcohol-induced pancreatitis within 2 years. In patients with mild biliary acute pancreatitis, cholecystectomy should be done before discharge. In patients with necrotising biliary acute pancreatitis, cholecystectomy should be postponed to prevent

infection until active inflammation subsides and fluid collections resolve or stabilize [1]. In patients who cannot undergo surgery, the recurrence rate can be greatly lowered by endoscopic sphincterotomy, with the aim of achieving spontaneous passage of any stones still present in the gallbladder [128].

Prophylactic stent placement and precut sphincterotomy is recommended to prevent postendoscopic retrograde cholangiopancreatography pancreatitis [20]. Findings from two meta-analyses [129, 130] show that prophylactic pancreatic stent placement reduces the risk of postendoscopic retrograde cholangiopancreatography pancreatitis. Indomethacin inhibits prostaglandin production in vivo, and is a powerful inhibitor of serum phospholipase A2 activity in acute pancreatitis. More than three decades ago, we showed that indomethacin given before or shortly after an acute pancreatitis attack was triggered markedly reduced mortality in rats [131]. Later, the application of indomethacin suppositories reduced the frequency and intensity of pain attacks in patients with acute pancreatitis [132]. This favourable effect of indomethacin was then forgotten, until the recommendation of routine rectal administration of 100 mg diclofenac or indomethacin immediately before or after endoscopic retrograde cholangiopancreatography [20] on the basis of findings from three meta-analyses [133, 134, 135]. By contrast, routine prophylactic use of nitroglycerin, cephtazidime, somatostatin, gabexate, ulinastatin, glucocorticoids, antioxidants, heparin, interleukin 10, pentoxifylline, semapimod, and the recombinant platelet-activating factor acetylhydrolase is not recommended [20]. The results of a network meta-analysis show that rectal non-steroidal anti-inflammatory drugs are better than pancreatic duct stents for the prevention of postendoscopic retrograde cholangiopancreatography pancreatitis [136].

Conclusions

From the pathophysiological viewpoint, the consensus has been that exposure of acinar cells to injurious agents (alcohol or bile salts) perturbs a multitude of acinar functions (exocytosis, enzyme activation, lysosomal function, cytokine production, mitochondrial function, and autophagy); however, findings from studies suggest that the final common mechanism that mediates acinar cell death (irrespective of the cause of acute pancreatitis) might be aberrant intracellular calcium signaling [44]. Novel evidence is accumulating to show that the pathogenesis of acute pancreatitis might not be limited to acinar cell perturbation alone, but that pancreatic stellate cells might also have a key early role, possibly via secretion of inflammatory mediators upon activation, by factors such as alcohol and its metabolites [32, 137].

With regard to the clinical management of acute pancreatitis, the Atlanta classification has been revised[46] and will have to stand the test of clinical application. The potential for new prognostic variables to assess severity of pancreatitis seems to be exhausted. Great promise is shown by the novel HAPS, which, by contrast with the existing variables, identifies patients whose pancreatitis is only mild and who therefore do not need intensive treatment. The past few years have seen particular interest in criteria for patient transfer, methods of fluid replacement and nutrition, and treatment of infected and sterile necrosis, with implications for clinical practice. Finally, attention has focused on the prevention of repeated episodes of pancreatitis by alcohol weaning after alcohol-induced acute pancreatitis and cholecystectomy before discharge in patients with mild biliary acute pancreatitis, together with prevention of postendoscopic retrograde cholangiopancreatography pancreatitis by means of rectal nonsteroidal anti-inflammatory drugs or pancreatic stents.

Contributors

All authors took part in the literature research, figure creation, data analysis and interpretation, and manuscript writing. PGL coordinated the project.

Declaration of interests

We declare no competing interests.

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Acute pancreatitis

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Acute pancreatitis, an inflammatory disorder of the pancreas, is the leading cause of admission to hospital for gastrointestinal disorders in the USA and many other countries. Gallstones and alcohol misuse are long-established risk factors, but several new causes have emerged that, together with new aspects of pathophysiology, improve understanding of the disorder. As incidence (and admission rates) of acute pancreatitis increase, so does the demand for effective management. We review how to manage patients with acute pancreatitis, paying attention to diagnosis, differential diagnosis, complications, prognostic factors, treatment, and prevention of second attacks, and the possible transition from acute to chronic pancreatitis.