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Acute pancreatitis

Seminar

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Abstract

Acute pancreatitis (AP), an inflammatory condition of the pancreas, is the leading cause of hospitalisation for gastrointestinal disorders in the USA and certainly also in many other countries. Gallstones and alcohol abuse are long-established risk factors, but more recently a number of new aetiological factors have emerged that, together with new aspects of pathophysiology, improve our understanding of AP. As incidence (and hospitalisation) rates for AP increase, so does the demand for effective management. Taking recent advances into account, we review how best to manage patients with AP, paying attention to diagnosis, differential diagnosis, complications, prognostic factors, treatment, and prevention of second attacks, as well as the possible transition from AP to chronic pancreatitis. (115 words)

Introduction

This Seminar is intended to provide a comprehensive, balanced account of the advances since the last Lancet seminar on acute pancreatitis (AP),¹ highlight areas of controversy or international differences in practice, and describe the underlying concepts.

The annual incidence of AP ranges from 13 to 45/100,000 persons (webappendix).² In the USA, among patients treated in hospital in 2009, AP was the most frequent principal discharge diagnosis in gastrointestinal disease and hepatology. The number of discharges with AP as principal diagnosis was 30% higher than in 2000. AP occupied places 2, 1 and 5, respectively, in the rankings of total hospital stays, aggregate costs and in-hospital deaths.³ Accurate data on AP are thus indispensable.

Search strategies and selection criteria. We searched the PubMed database for the term "acute pancreatitis" together with "aetiology", "pathogenesis", "prognostic parameters", "complications", "death", "treatment", or "prognosis". We accommodated articles in English, French, German, and Spanish from the past 5 years, together with commonly

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referenced and highly cited older publications that appeared necessary for full understanding. Moreover, we included several sets of guidelines, among them two that cover almost the whole gamut of AP, namely those from the American College of Gastroenterology (ACG) and the International Association of Pancreatology/American Pancreatic Association (IAP/APA).

**Aetiology**

Gallstones and alcohol abuse are the main risk factors for AP (details in webappendix). Over 20 or 30 years, however, the risk of biliary pancreatitis in patients with asymptomatic gallstones is unlikely to be more than 2%, and that of alcoholic pancreatitis in heavy drinkers is unlikely to exceed 2-3%. Other, possibly genetic, factors must therefore play a part (Table 1).

**Smoking.** Recent reports suggest that smoking may increase the risk of an attack of AP. While there was no association between smoking and biliary pancreatitis, the risk of non-gallstone-related AP was found to be more than double (RR = 2.29; 95% CI 1.63 to 3.22) among current smokers with ≥20 pack-years compared with never-smokers. Notably, in heavy smokers with ≥400 g monthly consumption of alcohol the risk was increased more than fourfold (RR = 4.12; 95% CI 1.98-8.60). Smoking duration rather than smoking intensity increased the risk. It was beneficial to stop smoking, but only after two decades was the risk comparable to that of non-smokers.

This Swedish study may indicate that smoking is an independent risk factor for AP, but there was residual confounding by other factors, plus missing alcohol intake data as limitations in their study.

**Drugs.** A recent review gives a useful overview of the current knowledge on drug-induced pancreatitis until 2011 and the substances involved (Table 1 and webappendix).
**Diabetes mellitus.** In four large retrospective studies, type 2 diabetes increased the risk of AP 1.86- to 2.89-fold.\(^{10-13}\) Compared with non-diabetics, the risk was particularly high in younger diabetics (ratio 5.26 under 45 years, 2.44 over 45 years).\(^{13}\) The excess risk was reduced by anti-diabetic medications.\(^{12}\) There is current debate regarding the possibility of incretin-based therapies leading to AP.\(^{14,15}\)

**Pancreas divisum.** It has long been debated whether failure of fusion of the dorsal and ventral pancreatic buds during gestation has any clinical or pathological consequences. In a group of patients with AP and chronic pancreatitis (CP) the prevalence of pancreas divisum was similar in those with and without idiopathic pancreatitis and alcoholic pancreatitis (7.5% and 7%, respectively); thus, pancreas divisum alone does not cause pancreatitis. However, associations between pancreas divisum and mutations of CFTR (cystic fibrosis transmembrane conductance regulator), SPINK1 (serine protease inhibitor Kazal-type 1), or PRSS1 (protease, serine 1) of 47%, 16% and 16% respectively, were observed suggesting a cumulative effect.\(^{16}\) This conclusion is problematic, because associations do not mean causation. Patients with pancreas divisum and CFTR mutations should be referred for genetic counselling, and endoscopic/surgical therapy should be withheld unless randomised studies show benefit.\(^{17}\)

**Endoscopic retrograde cholangiopancreatography (ERCP)**
Pancreatitis is the most frequent complication following ERCP (incidence 3.5% in unselected patients). It is mild or moderate in approximately 90% of cases. Independent patient- and procedure-related risk factors for post-ERCP pancreatitis (PEP) are listed in Table 2. Risk factors act synergistically.\(^{18}\)

**Single/double-balloon enteroscopy (SBE/DBE).** Both methods can result in hyperamylasaemia and AP, probably due to repeated stretching of the small-bowel and/or mesenteric ligaments. The rates of hyperamylasaemia are reported to be 17% and 16% for DBE and SBE,
respectively,\textsuperscript{19,20} but the rate of AP is much lower, (0 to 1%).\textsuperscript{19,20} Large prospective studies are required to ascertain the true incidence of AP and to potentially identify avoidable risk factors following DBE and SBE.

**Pathogenesis**

Pancreatic duct obstruction, regardless of the 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/autophagic vacuoles containing an admixture of digestive and lysosomal enzymes. The lysosomal enzyme cathepsin B can activate trypsinogen to trypsin. Notably, recent studies report lysosomal dysfunction in pancreatitis and an imbalance between the trypsinogen-activating isoform, cathepsin B, and the trypsin-degrading isoform, cathepsin L.\textsuperscript{21} 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\textsuperscript{22}). A block in the normal apical exocytosis of zymogen granules may also facilitate 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.\textsuperscript{23} Evidence supporting a role for premature trypsinogen activation and autodigestion in AP comes from the discovery in hereditary pancreatitis patients of a mutation in the trypsinogen gene resulting in the formation of active trypsin that is resistant to degradation.\textsuperscript{24} Supporting this, a recent study shows that genetically engineered mice lacking the trypsinogen 7 gene are protected from supramaximal caerulein-induced acinar injury.\textsuperscript{24}

Acinar injury due to autodigestive processes stimulates an inflammatory response (infiltration of neutrophils and macrophages, release of cytokines tumour necrosis factor-\(\alpha\) and interleukins 1, 6 and 8) within the pancreatic parenchyma. However, parenchymal inflammation has also been demonstrated in trypsinogen null mice after caerulein hyperstimulation.\textsuperscript{25}
suggesting that inflammatory infiltration can occur independent of trypsinogen activation. Whatever the stimulus for inflammation, in a minority of cases the reaction is severe with multi-organ failure and sepsis; the latter is particularly thought to result from an increased propensity for bacterial translocation from the gut lumen into the circulation.  

Recently, 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 and/or by a G-protein-coupled receptor for bile acids (Gpbar1). Once within the cell, bile acids increase intra-acinar calcium levels via inhibition of sarcoendoplasmic Ca\(^{++}\)-ATPase (SERCA) and activate signalling pathways including MAPK and PI3K and transcription factors such as NFkB, thereby inducing synthesis of proinflammatory mediators. However, whether these processes are important clinically remains unclear since clinical evidence for biliopancreatic reflux is scant.  

**Alcoholic pancreatitis.** Alcohol is known to exert direct toxic effects on the pancreas, but additional triggers or co-factors appear to be necessary to initiate overt pancreatitis.  

**Direct toxic effects of alcohol on the pancreas.** Early studies focussed on the effects of alcohol on the sphincter of Oddi (SO) as a possible mechanism of duct obstruction leading to pancreatitis (similar to that described for biliary pancreatitis). However, the results were controversial, with both decreased and increased SO tone reported. There is more consistent evidence that the effects of alcohol on small pancreatic ducts and the acinar cells themselves play a role in alcohol-induced pancreatic injury. Alcohol increases the propensity for precipitation of pancreatic secretions and the formation of protein plugs within pancreatic ducts owing to (i) alterations of lithostathine and glycoprotein 2, two non-digestive enzyme components of pancreatic juice with self-aggregation.
properties, and (ii) increased viscosity of pancreatic secretions due to CFTR dysfunction. The protein plugs enlarge and form calculi, causing ulceration of adjacent ductal epithelium, scarring, further obstruction and eventually acinar atrophy and fibrosis.

Experimental studies have shown that alcohol increases digestive and lysosomal enzyme content within acinar cells and destabilises the organelles that contain these enzymes, 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 likely a consequence 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 alterations in the intracellular redox state (14-22) (webappendix) (Fig. 1).

Alcohol also exerts toxic effects on pancreatic stellate cells (PSCs; resident cells of the pancreas that regulate extracellular matrix turnover in health). PSCs are activated by alcohol, its metabolites and oxidative stress to a myofibroblast-like phenotype that synthesises cytokines, which can also contribute to the inflammatory process during AP (Fig. 1).

**Individual susceptibility to alcoholic pancreatitis.** Despite the known detrimental effects of alcohol and its metabolites on the pancreas, only a minority of drinkers develop overt disease, prompting a search for the additional insult required for precipitating pancreatitis. Unfortunately, none of the candidate trigger factors investigated to date (diet, amount and type of alcohol consumed, pattern of alcohol consumption, hyperlipidaemia, smoking, inherited factors) has been shown to play an unequivocal role. The role of smoking in alcoholic AP is particularly controversial, because although animal studies have reported detrimental effects of cigarette smoke extract, nicotine and/or nicotine-derived nitrosamine ketone, NNK) on duct or acinar cells, the clinical relevance of these observations is mitigated by the very close association
between heavy smoking and heavy drinking, making it difficult to ascribe the initiation of AP in humans to smoking alone. Nevertheless, there is general consensus that smoking accelerates the progression of alcoholic pancreatitis. Bacterial endotoxinaemia is another possible trigger factor, given recent experimental evidence that an endotoxin challenge in alcohol-fed rats leads to AP, whereas alcohol feeding alone causes no damage. Since alcohol is known to increase gut permeability, an inability to detoxify circulating endotoxin may make some drinkers susceptible to overt disease.

In terms of inherited factors relevant to alcoholic pancreatitis, genetic factors related to digestive enzymes, trypsin inhibitors, cytokines, CFTR, MHC antigens, alcohol-metabolizing enzymes, oxidant stress-related proteins and detoxifying enzymes have failed to show an association. A recent genome-wide association study reported an association between overexpression of claudin 2 (CLDN2, a tight junction protein) and increased risk of alcoholic pancreatitis, with the protein overexpressed on the basolateral membranes of acinar cells in these patients. However, the functional significance of this observation remains unclear.

Signalling pathways in AP. A multitude of signalling pathways/molecules are perturbed within the acinar cell upon exposure to injurious agent(s), but accumulating evidence points to the final common mechanism for acinar injury being aberrant intracellular calcium signalling.

Classification

Attempts to revise the Atlanta classification go back many years. The recently published revised classification provides definitions of the clinical and radiologic severity of AP. Clinical severity is stratified into three categories: mild AP, moderately severe AP, and severe AP (Table 3).
Patients with mild AP (no organ failure or systemic or local complications) usually do not require pancreatic imaging and are frequently discharged within 3 to 7 days of onset of illness.

Moderately severe AP is characterised by one or more of the following features: transient organ failure (defined as organ failure lasting <48 h), systemic complications, or local complications. Organ failure includes respiratory, cardiovascular, and renal failure utilising the same criteria as in the Atlanta Symposium of 1992. The revised classification recommends that the modified Marshall scoring system be utilised to characterise the severity of failure of these three systems. Systemic complications are defined as an exacerbation of pre-existing comorbidities including congestive heart failure, chronic liver disease, and chronic lung disease. Local complications include complications of interstitial pancreatitis – peripancreatic fluid collections and pancreatic pseudocysts – and complications of necrotising pancreatitis – acute necrotic collections and walled-off necrosis (Table 4). Patients who experience moderately severe AP may require more extended hospitalisation and have a higher mortality than patients with mild AP.

Severe AP is characterised by the presence of persistent single or multiple organ failure (defined by organ failure that is present for ≥48 h). Most patients who experience persistent organ failure have pancreatic necrosis and have a mortality of at least 30%.

An alternative stratification of AP severity has been proposed that includes four categories rather than three (Table 3). These are mild (absence of necrosis or organ failure), moderate (sterile necrosis and/or transient organ failure), severe (infected necrosis or persistent organ failure), and critical (infected necrosis and persistent organ failure). Studies will be required to determine whether it is more clinically relevant to stratify patients into three or four categories of severity.

Regarding radiologic severity of AP, the revised classification provides detailed definitions of the imaging features of AP. 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 which does not resolve may 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 radiologic definition of acute necrotic collections and walled-off necrosis. In the past, the site of acute necrotic collections in necrotising pancreatitis was thought to involve the pancreatic parenchyma and peripancreatic tissue or in rare occasions only the pancreatic parenchyma. It is now recognised that acute necrotic collection may involve only the peripancreatic tissue. Patients with peripancreatic necrosis have an increased morbidity and mortality compared to interstitial pancreatitis. Acute necrotic collections in necrotising pancreatitis may be sterile or infected. The natural history of acute necrotic collections is variable. They can become smaller and on rare occasions disappear completely. Most often, acute necrotic collections develop a well-defined inflammatory wall surrounding varying amounts of fluid and necrotic debris, termed walled-off necrosis, which may be either sterile or infected.

This revised classification requires testing to evaluate its clinical usefulness. It would be reasonable to expect that this revised classification of AP will undergo further revisions in the future.

Clinical signs and symptoms

Clinical presentation and physical examination as well as the essential abdominal and systemic complications of AP are listed in the webappendix.

Diagnosis

Confirmation of diagnosis. The primary aim is confirmation of the diagnosis and exclusion of differential diagnoses (webappendix).
According to the revised Atlanta classification, AP can be diagnosed if at least two of the following three criteria are fulfilled: (1) abdominal pain (acute onset of persistent, severe epigastric pain often radiating to the back); (2) serum lipase (or amylase) activity at least three times the upper limit of normal; (3) characteristic findings of AP on contrast-enhanced computed tomography (CECT) and, less commonly, magnetic resonance imaging (MRI) or transabdominal ultrasonography. Diagnostic imaging is essential in patients with a slight enzyme elevation (webappendix).

Importantly, pancreatic enzyme levels on admission are not correlated with disease severity. The disease can be serious, even fatal, although the enzymes are only slightly elevated (below three times normal).

**Supplementary diagnostic procedures**

**Laboratory tests.** In addition to serum amylase and/or lipase, the following parameters should be established on admission: complete blood count without differential, electrolytes, blood urea nitrogen (BUN), creatinine, serum glutamic pyruvic transaminase (SGPT), serum glutamic oxalic transaminase (SGOT), alkaline phosphatase (AP), blood sugar, coagulation status, total albumin. Arterial blood gas analysis is generally indicated whenever oxygen saturation is below 95% or the patient is tachypnoeic.

The frequency of repeat determinations depends on the clinical course.

**ECG.** In ≤50% of cases ST segment elevations and negativities are registered, mainly in the posterior wall, without myocardial infarction.

**Chest X-ray in two planes.** Pleural effusions and/or pulmonary infiltrates are signs of severe disease.

**Abdominal panoramic X-ray (upright or left lateral position).** Ileus is shown by a sentinel loop (isolated bowel loop in left upper or middle abdomen) or colon cut-off sign (lack of air in left colonic flexure or descending colon). Pancreatic calcifications represent proof of CP, i.e., the
patient is suffering from an episode of AP superimposed on CP rather than a first attack of AP.

**Computed tomography.** Unenhanced CT scoring systems evaluate the extent of pancreatic and peripancreatic inflammatory changes [Balthazar score,\(^{47}\) pancreatic size index (PSI) \(^{48}\)] or evaluate both peripancreatic inflammatory changes and extrapancreatic complications [mesenteric oedema and peritoneal fluid (MOP) score,\(^{49}\) extrapancreatic (EP) score,\(^{50}\) extrapancreatic inflammation on CT (EPIC) score].\(^{51}\)

Two CT scoring systems require intravenous contrast agents to determine the presence and extent of pancreatic parenchymal necrosis. The CT severity index (CTSI)\(^{52}\) combines quantification of extrapancreatic inflammation with extent of pancreatic necrosis, while the modified CTSI (MCTSI)\(^{53}\) assigns points for extrapancreatic (e.g. vascular, gastrointestinal or extrapancreatic parenchymal) complications and presence of pleural effusions and/or ascites.

Contrast-enhanced CT is the gold standard for diagnostic imaging to help determine disease severity. (Axial contrast-enhanced CTs of the pancreas of a patient with AP on admission and 1, 10 and 20 days later are shown in the webappendix).

However, the predictive accuracy of CT scoring systems for severity of AP is similar to clinical scoring systems. Hence, a CT on admission solely for severity assessment in AP is not recommended.\(^{54}\) An early CT, i.e. performed within the first 4 full days after symptom onset (days 0—4), has not been shown to reveal an alternative diagnosis, help with the distinction of interstitial versus necrotising pancreatitis, or provide evidence of an important complication.\(^{55}\) Hence, an early CT should only be obtained when there is clinical doubt about the diagnosis of AP, and other life-threatening conditions must be excluded.
Prognostic parameters

The existing scoring systems (webappendix) seem to have reached their maximal efficacy in predicting persistent organ failure in AP. Sophisticated combinations of predictive rules are more accurate but cumbersome, and therefore of limited clinical use. New approaches are needed.56

One such approach is the Harmless Acute Pancreatitis Score (HAPS), which enables identification of mild cases of AP (the great majority) within 30 min of inpatient admission, even by non-specialists. Two prospective studies, one monocentric and one multicentric, showed that mild AP can be predicted with 98% accuracy in patients with no rebound tenderness and/or guarding, normal haematocrit, and normal serum creatinine.57 Studies from Sweden and India confirm the accuracy of the HAPS.58,59 This score thus identifies the majority of patients who neither have, nor will, develop necrotising pancreatitis or organ failure and will therefore not need intensive care. The HAPS can be used in the community care setting, where the treating physician can triage the patients who require early transfer to more specialised centres for more aggressive management and meticulous monitoring.59 It may even be able to determine whether the patient could be cared for adequately and more economically as an outpatient.

Therapy

Initial management. The patient’s management begins on the emergency ward, where AP must be confirmed, the risk stratified, and basic treatment initiated. The last-named comprises early fluid resuscitation, analgesia, and nutritional support (webappendix).

Fluid resuscitation. Patients undergoing volume resuscitation should have the head of the bed elevated, undergo continuous pulse oximetry, and receive supplemental oxygen; this last-named measure more than halved mortality in patients over 60.60
In experimental pancreatitis, pancreatic microvascular perfusion is reduced, and this is aggravated by arterial hypotension. The situation in humans, however, remains unclear. Neither comparisons of aggressive versus nonaggressive resuscitation protocols (4 vs 3.5 L within the first 24 h) nor goal-directed fluid therapy (goals included blood urea nitrogen, central venous pressure, haematocrit, heart rate, blood pressure, and urine output) yielded clear results. One retrospective study showed that early fluid resuscitation was associated with reduced incidence of systemic inflammatory response syndrome (SIRS) and organ failure at 72 h, but too little fluid is just as deleterious as too much. In one study rapid haemodilution increased the incidence of sepsis within 28 days and in-hospital mortality. In another, the administration of a small amount of fluid was not associated with a poor outcome, but the need for a large amount was.

With regard to what should be infused, the recommendations of the ACG and IAP/APA guidelines are very similar: the former suggests that lactated Ringer’s solution may be preferred to isotonic crystalloid replacement fluid, the latter simply states: Ringer’s lactate for initial fluid resuscitation must not be given, however, to the rare patients with hypercalcaemia. The two sets of guidelines differ with regard to rate of infusion: ACG 250—500 ml/h, IAP/APA 5—10 ml/kg/h. Assuming the ACG recommendation is for a patient weighing 70 kg, following the IAP/APA guideline would lead to a much higher rate of infusion, 50—700 ml/h. Only the ACG makes a firm recommendation as to when infusion should begin: early aggressive intravenous hydration is most beneficial in the first 12—24 h and may have little benefit beyond this time.

These recommendations are based essentially on a prospective multicentre randomised study in which resuscitation with lactated Ringer’s solution reduced by 84% during the first 24 h, compared with normal saline. In this study, infusion started with a bolus of 20 ml/kg body weight 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 parameter is BUN because studies have shown that an elevated BUN at admission and an increase in BUN during the first 24 h are independent risk factors for mortality in acute pancreatitis.68-70 The recommendation has been made to adjust fluid resuscitation during the first 24 h based on whether the BUN increases or decreases.71

**Pain treatment.** This has absolute priority on admission. Unfortunately, a recent 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.72 Until a conclusive study is published, the prevailing guidelines for acute pain management in the perioperative setting should be followed.73

**Patient transfer.** Patients in high-volume centres (≥118 admissions/year) have a 25% lower relative risk of death than those in low-volume centres.74 Thus, patients who fail to respond to early resuscitation and/or display persisting organ failure or extensive local complications should be transferred to a pancreatitis centre (if available) with multidisciplinary expertise including therapeutic endoscopy, interventional radiology, and surgery. Patients with persistent SIRS, increased levels 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 the HAPS57 predicts harmless AP, can be treated on a general ward.

**Nutrition.** In mild AP, oral feedings can be started if there is no nausea and vomiting, and abdominal pain has resolved.65 A systematic review of 15 RCTs 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! 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 multiple organ failure, pancreatic infectious complications, and mortality.

Numerous studies have proposed administering enteral nutrition via a nasoduodenal rather than nasojejunal tube, but a firm recommendation cannot yet be given. An initial attempt at nasoduodenal intubation seems advisable, but the pancreatic head inflammation in severe AP may cause duodenal stenosis, necessitating endoscopic placement.

Nausea and vomiting owing to persisting gastroparesis, ileus or postprandial pain indicates parenteral nutrition via a central venous catheter.

Glutamine supplementation (GS) has been discussed for patients with critical AP leading to catabolism. A meta-analysis of 12 RCTs revealed that GS 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 GS was attributed to the fact that glutamine is largely metabolised in the gut and the liver so that the plasma glutamine level is lower after enteral than intravenous administration.

**Antioxidant therapy.** Treatment with antioxidants is ineffective.

**Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES).** A recent Cochrane review found no evidence that routine early ERCP significantly affects mortality and local or systemic complications in patients with acute gallstone pancreatitis, regardless of predicted severity. The results, however, support current recommendations that early ERCP be considered in patients with co-existing cholangitis or biliary obstruction.

**Management of local complications**
Prophylactic antibiotics. Prophylactic antibiotics are not indicated.86-89

Necrosis. Surgical resection of pancreatic necroses can be achieved by open, laparoscopic, or “staged” necrosectomy (open staged lavage, closed continuous lavage). These methods do not compete but rather complement other techniques. No guidelines exist, but there is consensus that surgical intervention should be performed — if at all — at a later stage.90

More conservative interventions now predominate91,92 as a result of two pioneering advances.

First, it has been shown that antibiotic treatment alone can heal infected necrosis.93 This is now the first step when such lesions are confirmed. Antibiotic treatment is possible in almost two-thirds of patients with necrotising pancreatitis, with mortality of 7%.94

Second, Seifert et al.95 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.96 Endoscopic transgastric necrosectomy compares favourably with surgical approach.97

Clinical trials are needed to validate the various options for intervention.

Step-up management of infected necrosis (placement of percutaneous catheters in addition to treatment with antibiotics, if necessary followed by minimally invasive necrosectomy) was compared with open necrosectomy. This approach reduced new-onset multiple-organ failure by 29%. However, the study was underpowered to detect a difference in mortality.98

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).71 In this case direct endoscopic necrosectomy is possible in skilled hands.99

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**Pseudocyst.** The prognostic factors for the development of pseudocysts are alcohol abuse and initially severe disease. Spontaneous resolution occurs in every third patient with a pseudocyst. Prognostic factors for this are no or mild symptoms and pseudocyst diameter of ≤4 cm. Symptomatic pseudocysts may be successfully decompressed by endoscopic cystogastrostomy with endoscopic ultrasound guidance.

**Ductal disruption.** This can result in unilateral pleural effusion, pancreatic ascites, or enlarging fluid collection. If the disruption is focal, placement of a bridging stent via ERCP usually promotes duct healing. When ductal disruption occurs in an area of extensive necrosis, optimal management requires a multidisciplinary team of therapeutic endoscopists, interventional radiologists and surgeons.

**Peripancreatic vascular complications.** Splenic vein thrombosis has been reported in up to 20% of AP patients undergoing imaging. The risk of bleeding from gastric varices is < 5% and splenectomy is not recommended. Pseudoaneurysms are rare but cause serious complications in 4—10% of cases. Mesenteric angiography with transcatheter arterial embolisation is the first-line treatment.

**Management of extrapancreatic complications.** Extrapancreatic infections such as bloodstream infections, pneumonia and urinary tract infections occur early in up to 24% of AP patients and may double mortality. 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 or *Clostridium difficile* infection.

**Aftercare**

**Refeeding.** It is generally recommended to continue basic treatment until the patient shows distinct clinical improvement (freedom from pain, normal body temperature, normal abdominal findings). There is no
binding recommendation for severe AP; the decision is taken on an individual basis. In mild AP the current ESPEN guidelines should be followed: resumption of oral feeding as soon as possible.\textsuperscript{110} When and how that is remains undefined. What is certain is that the beginning of refeeding does not depend on the normalisation of lipase.\textsuperscript{111} It is perhaps best to leave the decision to the patients, i.e., they can eat when they are hungry.\textsuperscript{111, 112} Positive experience has been reported with widely varying diets: unspecified,\textsuperscript{113} soft diet,\textsuperscript{114} full diet with\textsuperscript{115} or without\textsuperscript{116} fat restriction.

Unfortunately, however, oral refeeding can lead to pain relapse and therefore to a longer hospital stay (webappendix).

**Imaging procedures.** Patients with AP of unknown origin should undergo endosonography (EUS) to exclude stones or sludge in the gall bladder or bile ducts. EUS or magnetic resonance cholangiopancreatography (MRCP) may be indicated to exclude a tumour. Tumour-related AP can appear to heal before flaring up again.\textsuperscript{117}

**Transient exocrine/endocrine pancreatic insufficiency.** Both can occur during healing.\textsuperscript{118-120} Monitoring is therefore advisable. Pancreatic function is generally normal again 3 months after abatement of AP. Pancreatic enzyme substitution is not usually necessary, but may be required temporarily after a severe attack.

Endocrine pancreatic function should be checked after about 3 months (fasting and postprandial blood sugar, possibly HbA\textsubscript{1C} determination). Severe AP is often followed by diabetes mellitus.\textsuperscript{121}

**Transition to chronic pancreatitis.** In a German study over a period of almost 8 years, only alcoholics developed CP, independently of both severity of first AP and discontinuation of alcohol and nicotine.\textsuperscript{122} The cumulative risk of developing CP was 13% within 10 years, 16% within 20 years. The risk of CP in those who survived the second attack of AP was 38% within 2 years. Nicotine abuse increased the risk significantly.\textsuperscript{122}
Similar investigations from Denmark and the USA showed a transition to CP in 24.1% of cases after 3.5 years and in 32.3% after 3.4 years. In both studies transition was also occasionally seen in patients with non-alcohol-induced pancreatitis.

Ductal scarring can be seen on ERCP even after healing but must under no circumstances lead to diagnosis of CP and substitution of pancreatic enzymes.

Prevention

**Alcohol weaning.** After years of resignation in the face of alcoholism, a study showed that interventions by medical personnel at 6-month intervals significantly lowered the recurrence rate of alcohol-induced pancreatitis within 2 years.

**Cholecystectomy.** In patients with mild biliary AP, cholecystectomy should be performed before discharge. In patients with necrotising biliary AP, cholecystectomy should be postponed in order to prevent infection until active inflammation subsides and fluid collections resolve or stabilise.

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 gall bladder.

**Post-ERCP pancreatitis.** Prophylactic stent placement and pre-cut sphincterotomy is recommended to prevent PEP. Two meta-analyses show that prophylactic pancreatic stent placement indeed reduces the risk of PEP.

Indomethacin inhibits prostaglandin production in vivo and is a powerful inhibitor of serum phospholipase A2 activity in AP. Over three decades ago one of us demonstrated that indomethacin administered before or shortly after the triggering of an AP attack in rats markedly reduced mortality. Later, the application of indomethacin suppositories reduced the frequency and intensity of pain attacks in patients with AP. This favourable effect...
of indomethacin was then forgotten, until the recent recommendation of routine rectal administration of 100 mg diclofenac or indomethacin immediately before or after ERCP\textsuperscript{18} on the basis of three meta-analyses.\textsuperscript{131-133} In contrast, routine prophylactic use of nitroglycerin, cephazidime, somatostatin, gabexate, ulinastatin, glucocorticoids, antioxidants, heparin, interleukin-10, pentoxifylline, semapimod, and the recombinant platelet-activating factor acetylhydrolase is not recommended.\textsuperscript{18}

The results of a network meta-analysis indicate that rectal non-steroidal anti-inflammatory drugs alone are superior to pancreatic duct stents alone in preventing PEP.\textsuperscript{134}

**Conclusions**

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

With regard to the clinical management of AP, the Atlanta classification has been revised and will have to stand the test of clinical application. The potential for new prognostic parameters to assess severity of pancreatitis appears to be exhausted. Great promise is shown by the novel harmless acute pancreatitis score, which in contrast to the existing parameters identifies the patients whose pancreatitis is only mild and who therefore do not require intensive treatment.
The past few years have seen particular interest in criteria for patient transfer, in methods of fluid replacement and nutrition, and in the treatment of infected and sterile necrosis, with implications for clinical practice. Finally, the prevention of repeated episodes of pancreatitis by alcohol weaning after alcohol-induced AP and by cholecystectomy before discharge in patients with mild biliary AP has come to the fore, together with prevention of post-ERCP pancreatitis by means of rectal nonsteroidal anti-inflammatory drugs or pancreatic stents. \textit{(5499 words)}

**Authors Contributions**

Paul Georg Lankisch: Literature research, figures, data analysis, data interpretation, writing and project coordination

Minoti Apte: Literature research, figures, data analysis, data interpretation, and writing

Peter Banks: Literature research, figures, data analysis, data interpretation, and writing
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Table 1. Drugs for which a definite or probable association with AP has been reported (up to 2011) (modified to Nitsche et al.9)

<table>
<thead>
<tr>
<th>Definite association to AP</th>
<th>Probable association to AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Atorvastatine</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>Carboplatin/Docetaxel</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Didanosine</td>
</tr>
<tr>
<td>Carbomazepine</td>
<td>Doxycycline</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Enalapril</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Famotidine</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Ifosfamide</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Liraglutide</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Maprotiline</td>
</tr>
<tr>
<td>Oestrogens</td>
<td>Mesalazine</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Orlitostat</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Oxaliplatin</td>
</tr>
<tr>
<td>Interferon-α2b</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Itroconazol</td>
<td>Secnidazole</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Sitagliptine</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Mesalamine/olsalazine</td>
<td>Tigecyclin</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Vildagliptine</td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
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<tr>
<td>Octreotide</td>
<td></td>
</tr>
<tr>
<td>Olanzepine</td>
<td></td>
</tr>
<tr>
<td>Opiates</td>
<td></td>
</tr>
<tr>
<td>Oxyphenbutazone</td>
<td></td>
</tr>
<tr>
<td>Pentamidine</td>
<td></td>
</tr>
<tr>
<td>Pentavalent anti-moniais</td>
<td></td>
</tr>
<tr>
<td>Penformin</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td></td>
</tr>
<tr>
<td>Sulfmethaxazole/Trimethoprim</td>
<td></td>
</tr>
<tr>
<td>Sulindac</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Independent risk factors for post-ERCP pancreatitis (PEP)\(^8\)

<table>
<thead>
<tr>
<th>Patient-related risk factors</th>
<th>Adjusted odds ratios (95% CI in parentheses, except where indicated otherwise)</th>
<th>Pooled incidence of PEP in patients with vs. those without risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected sphincter of Oddi dysfunction</td>
<td>4.09 (3.37—4.96)</td>
<td>10.3% vs. 3.9%</td>
</tr>
<tr>
<td>Female gender</td>
<td>2.23 (1.75—2.84)</td>
<td>4.0% vs. 2.1%</td>
</tr>
<tr>
<td>Previous pancreatitis</td>
<td>2.46 (1.93—3.12)</td>
<td>6.7% vs. 3.8%</td>
</tr>
<tr>
<td><strong>Likely risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger age</td>
<td>1.09—2.87 (range 1.09—6.68)</td>
<td>6.1% vs. 2.4%</td>
</tr>
<tr>
<td>Non-dilated extrahepatic bile ducts</td>
<td>Not reported</td>
<td>6.5% vs. 6.7%</td>
</tr>
<tr>
<td>Absence of CP</td>
<td>1.87 (1.00—3.48)</td>
<td>4.0% vs. 3.1%</td>
</tr>
<tr>
<td>Normal serum bilirubin</td>
<td>1.89 (1.22—2.93)</td>
<td>10.0% vs. 4.2%</td>
</tr>
<tr>
<td><strong>Procedure-related risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Definite risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precut sphincterotomy</td>
<td>2.71 (2.02—3.63)</td>
<td>5.3% vs. 3.1%</td>
</tr>
<tr>
<td>Pancreatic injection</td>
<td>2.2 (1.60—3.01)</td>
<td>3.3% vs. 1.7%</td>
</tr>
<tr>
<td><strong>Likely risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High number of cannulation attempts</td>
<td>2.40—3.41 (range 1.07—5.67)</td>
<td>3.7% vs. 2.3%</td>
</tr>
<tr>
<td>Pancreatic sphincterotomy</td>
<td>3.07 (1.64—5.75)</td>
<td>2.6% vs. 2.3%</td>
</tr>
<tr>
<td>Biliary balloon sphincter dilation</td>
<td>4.51 (1.51—13.46)</td>
<td>9.3% vs. 1.9%</td>
</tr>
<tr>
<td>Failure to clear bile duct stones</td>
<td>3.35 (1.33—9.10)</td>
<td>1.7% vs. 1.6%</td>
</tr>
</tbody>
</table>

ERCP, endoscopic retrograde cholangiopancreatography; CI, confidence interval
### Table 3. Definition of severity in AP: comparison of Atlanta and recent revisions

<table>
<thead>
<tr>
<th>Atlanta classification 1992(^\text{1})</th>
<th>Revised Atlanta classification 2012(^\text{4})</th>
<th>Determinant-based classification 2012(^\text{45})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild AP</strong></td>
<td><strong>Mild AP</strong></td>
<td><strong>Mild AP</strong></td>
</tr>
<tr>
<td>➢ No organ failure</td>
<td>➢ No organ failure</td>
<td>➢ No (peri)pancreatic necrosis and</td>
</tr>
<tr>
<td>➢ No local complications</td>
<td>➢ No local or systemic complications</td>
<td>➢ No organ failure</td>
</tr>
<tr>
<td><strong>Moderately severe AP</strong></td>
<td><strong>Moderately severe AP</strong></td>
<td><strong>Moderately severe AP</strong></td>
</tr>
<tr>
<td>➢ Transient organ failure (&lt;48 h)</td>
<td>➢ Transient organ failure (&lt;48 h)</td>
<td>➢ Sterile (peri)pancreatic necrosis and/or</td>
</tr>
<tr>
<td>and/or</td>
<td>➢ Local or systemic complications without persistent organ failure (&gt;48 h)</td>
<td>➢ Transient organ failure (&lt;48 h)</td>
</tr>
<tr>
<td>➢ Local or systemic complications</td>
<td>➢ Local or systemic complications without persistent organ failure (&gt;48 h)</td>
<td></td>
</tr>
<tr>
<td><strong>Severe AP</strong></td>
<td><strong>Severe AP</strong></td>
<td><strong>Severe AP</strong></td>
</tr>
<tr>
<td>➢ Local complications and/or</td>
<td>➢ Persistent organ failure (&gt;48 h)*</td>
<td>➢ Infected (peri)pancreatic necroses or</td>
</tr>
<tr>
<td>➢ Organ failure</td>
<td>➢ Single organ failure</td>
<td>➢ Persistent organ failure (&gt;48 h)</td>
</tr>
<tr>
<td>➢ PaO(_2) ≤60%</td>
<td>➢ Multiple organ failure</td>
<td></td>
</tr>
<tr>
<td>➢ Creatinine ≥2 mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Shock (systolic blood pressure ≤60 mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Gastrointestinal bleeding (&gt;500 ml/24 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Severe AP</strong></td>
<td><strong>Severe AP</strong></td>
<td><strong>Severe AP</strong></td>
</tr>
<tr>
<td>➢ Infected (peri)pancreatic necroses</td>
<td>➢ Infected (peri)pancreatic necroses or</td>
<td><strong>Critical AP</strong></td>
</tr>
<tr>
<td>or</td>
<td>➢ Persistent organ failure (&gt;48 h)</td>
<td>➢ Infected (peri)pancreatic necroses and</td>
</tr>
<tr>
<td>➢ Persistent organ failure (&gt;48 h)</td>
<td></td>
<td>➢ Persistent organ failure</td>
</tr>
</tbody>
</table>

*Persistent organ failure is now defined by a modified Marshall score\(^\text{135}\) (webappendix)
**Table 4 Revised definitions of morphological features of AP**  
(With permission of the publisher)

| 1. 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) |
| 2. 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) |
| 3. APFC (acute pancreatitis 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) |
| 4. Pancreatic pseudocyst | An encapsulated collection of fluid with a well-defined inflammation wall usually outside the pancreas with minimal or no necrosis. This entity usually occurs more than 4 weeks after onset of interstitial oedematous pancreatitis  
**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 AP, occurs after interstitial oedematous pancreatitis |
| 5. 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 tissue  
**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 |
6. 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 locations (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
Figure legend

**Fig. 1.** The effects of alcohol on the pancreatic acinar cell and the pancreatic stellate cell, based on experimental in vitro and in vivo evidence.

A) Pancreatic acinar cells metabolise alcohol via both oxidative and non-oxidative pathways and exhibit changes which predispose the cells to autodigestive injury, necroinflammation and cell death. These include:

1. Destabilisation of lysosomes and zymogen granules (mediated by oxidant stress [reactive oxygen species, ROS], cholesteryl esters [CE], fatty acid ethyl esters [FAEE] and decreased glycoprotein 2 [GP2], a major structural component of zymogen membranes)
2. Increased digestive and lysosomal enzyme content (due to increased synthesis [increased mRNA] and impaired secretion)
3. Increased activation of transcription factors (NFkB and AP-1) which regulate cytokine expression
4. A sustained increase in cytoplasmic calcium (Ca++) and mitochondrial calcium overload leading to mitochondrial depolarisation

B) Pancreatic stellate cells have the capacity to oxidise alcohol to acetaldehyde and this is associated with the generation of reactive oxygen species leading to oxidant stress. PSCs are activated upon exposure to alcohol to a myofibroblast-like phenotype stimulating the synthesis of proinflammatory mediators and cytokines by the cells.

The above changes sensitise the gland such that in the presence of an appropriate trigger/cofactor, overt injury is initiated.

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