Acute pancreatitis

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Acute pancreatitis is an important and extremely common cause of acute hospital admission which may be associated with major morbidity and mortality. Modern treatment is largely supportive with a limited role for surgery.

Acute pancreatitis is an acute inflammatory process of the pancreas, with variable involvement of other regional tissues or remote organ systems. Acute pancreatitis accounts for 3% of all cases of abdominal pain admitted to hospitals in the UK. Groups affected depend on the aetiology with a high incidence of alcoholic pancreatitis among young people in urban and socially disadvantaged communities, whereas the incidence is highest in older patients as a result of gall-stone disease in rural or more affluent populations. The UK incidence is between 21 and 283 cases per million population, and is increasing. Mortality has stayed at 10–15% for the last 20 years (British Society of Gastroenterology (BSG) Working Party, 1998).

Alcohol and gall-stones account for 25% and 45% of cases respectively. Other rarer causes of acute pancreatitis are shown in *Table 1*. Importantly up to 25% of cases are idiopathic.

The mechanism by which gall-stones cause acute pancreatitis was postulated by Halsted and Opie to be the result of an impaction of a gall-stone just proximal to the sphincter of Oddi (the so-called 'common channel' hypothesis) resulting in backflow of obstructed bile into the pancreatic duct (Opie, 1901). More modern hypotheses centre on obstruction of the pancreatic duct alone, either by obstruction within the duct or by transmitted pressure from an engorged or blocked biliary system. This obstruction is exacerbated by an increase in intraductal pressure (so-called 'obstruction stimulation' hypothesis) which triggers crinophagy whereby intra-cytoplasmic digestion of the contents of secretory vacuoles causing premature enzyme activation within the cells leading to autodigestion and damage to pancreatic tissue. The proposed mechanisms whereby alcohol induces acute pancreatitis include direct cellular toxicity, duodenopancreatic reflux, hyperstimulation of the pancreas and by causing immaturity in the subcellular membranes promoting crinophagy.

PATHOPHYSIOLOGY

The pathophysiology of acute pancreatitis involves a local and systemic inflammatory response. At a local level, cell membrane disruption is followed by extravascular migration of leucocytes, platelets and fibrin. Oedema and microvascular thrombosis follow. Inflammatory ascites accumulates and fat necrosis produces peritoneal 'studs'. The systemic inflammatory response derives mainly from leucocyte-derived cytokines and enzymes which mediate remote organ damage and also further pancreatic damage.

OUTLINE OF MANAGEMENT

The BSG (1998) guidelines suggested that management of acute pancreatitis can be broadly

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TABLE 1.
Causes of acute pancreatitis

Obstruction with or without hyperstimulation	Gall-stones*
	Intraduct parasites
	Afferent loop obstruction, after gastric surgery
	Periampullary tumours
	Choledochal cysts, in childhood
	Pancreas divisum
	Scorpion venom
Toxic and metabolic	Alcohol*
	Hyperlipidaemia
	Hypercalcaemia
	Uraemia
	Drugs, e.g. thiazide diuretics
	Hypotension or hypothermia
	Nutritional, e.g. anorexia
Iatrogenic	Endoscopic retrograde cholangiopancreatography
Trauma	Especially blunt trauma causing fracture against spine
Miscellaneous	Infections, e.g. mumps
	Hereditary
	Vasculitis
Idiopathic*	About 25% of cases are idiopathic

*common causes

divided into three overlapping phases. The first phase involves diagnosis and assessing severity. The second phase involves management according to severity with ongoing monitoring and assessment. The third phase is detecting and managing complications, and addressing aetiological factors.

DIAGNOSIS

The BSG (1998) guidelines suggested a diagnosis of acute pancreatitis should be made within 48 hours of admission. Full investigation is needed to rule out alternate life-threatening pathology.

CLINICAL FEATURES

History

Patients usually have rapid onset of severe upper abdominal pain often radiating to the back and associated with nausea or vomiting.

Physical examination

Mild pyrexia and tachycardia are common and generally the patient is distressed and dehydrated. Jaundice may be present. Abdominal examination reveals epigastric or generalized tenderness. Abdominal echymoses are often discussed but only occasionally present: Cullen's sign (periumbilical echymosis) may also occur in ruptured ectopic pregnancy and Grey Turner's sign (flank echymosis) can occur in ruptured aortic aneurysm. Disseminated fat necrosis may rarely produce paniculitis, a palpable thickening in the superficial fascia, and can cause arthralgia. Sometimes there is an obscure clinical picture, for instance in postoperative patients.

Biochemical

Where clinically appropriate, acute pancreatitis is diagnosed with a serum amylase four times above normal. However, isolated hyperamylasaemia lacks specificity as false positives can occur in visceral perforation, small bowel infarction, leaking aortic aneurysm and ectopic pregnancy. Renal clearance of amylase is reduced in uraemia. False negatives occur when measured late and where there is complete pancreatic necrosis. In alcohol-related attacks previous pancreatic damage causes a slower rise and lower peak. Hyperlipoproteinaemia masks detection. Pancreas-specific isoamylase is not commonly available.

An equivocal serum amylase is often accompanied by a diagnostic urinary amylase. Serum lipase is diagnostic when greater than twice the upper limit of normal. Lipase remains elevated longer than amylase and the only source is the pancreas. It is not frequently available. Trypsinogen activation peptide is under evaluation. Human chorionic gonadotrophin measurement excludes pregnancy in females.

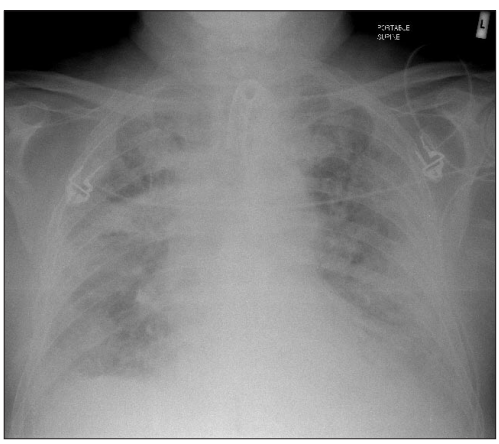

Figure 1. Chest X-ray showing acute respiratory distress syndrome.

Radiological

Plain X-rays: Chest and abdominal plain films provide a baseline and exclude other pathology, e.g. perforated viscus or intestinal obstruction. Abdominal X-ray findings are not specific, e.g. generalized or local ileus (sentinel loop), colon cut-off and renal halo. Retroperitoneal gas may indicate infection and calcified gall-stones or pancreatic calcification may be seen which indicates chronic changes or rarely tumour. Chest findings range from a pleural effusion to diffuse alveolar interstitial shadowing suggesting acute respiratory distress syndrome (*Figure 1*) in severe cases as a result of acute pancreatitis.

Ultrasound: A swollen pancreas may confirm diagnosis but is poorly visualized in 25–50% of cases. A dilated common bile duct, gall-stones, free peritoneal fluid and occasionally other relevant pathology can be seen.

Other modalities: Computed tomography (CT) with intravenous contrast may be diagnostic when there is clinical and biochemical uncertainty. Interventional radiology allows sampling of peritoneal fluid detected in the absence of other biochemical or radiological signs of pancreatitis. High amylase content suggests pancreatitis. Microscopy may suggest perforation if bacterial contamination exists.

Surgical

Laparotomy or laparoscopy may reveal pancreatitis when clinical suspicion of peritonitis is high and other tests are inconclusive. Diagnosis is sometimes made at autopsy.

PREDICTING SEVERITY

Definitions

Severe acute pancreatitis is associated with organ failure and/or local complications such as

necrosis ('sterile' or associated with infection), pseudocyst or abscess. Mortality is approximately 30% (Imrie, 1997).

Mild acute pancreatitis is associated with minimal organ dysfunction and an uneventful recovery. The predominant pathological feature is interstitial oedema. Around 80% of cases are mild.

Prediction of severity is useful for management and prognostic purposes, however, prediction is difficult and only becomes fact in retrospect.

Clinical assessment is only 50% accurate, but any evidence of organ failure indicates a severe attack.

Biochemical and objective criteria

These are useful for predicting severity but do not predict the need for subsequent surgery.

Imrie (Glasgow) and Ranson scoring (*Tables 2* and *3*) are multifactorial scoring systems and improve the accuracy of predicting severity to 70–80%. The Imrie criteria have been validated for the UK population (Blamey et al, 1984). Ranson criteria are similar: five are measured at initial admission and the other six within 48 hours (Ranson et al, 1974). A score of 3 or more on initial results and repeat tests over 48 hours predicts severe disease.

APACHE II (*Table 4*) – the Acute Physiology and Chronic Health Evaluation score – is based on 12 physiological variables, age, history of organ system insufficiency or immunocompromised state (Knaus et al, 1985). It allows prediction of severity on admission, a score of 9 or more being severe. APACHE II score can be used for daily assessment.

Blood C-reactive protein (CRP) concentration is 80% accurate with a peak level of 240 mg/litre in the first 4 days or a level of >120 mg/litre at the end of 1 week predicting a severe attack.

Other blood markers are not yet routine: inflammatory (e.g. interleukin 6), enzymatic (e.g. trypsinogen activation peptide) and non-specific markers (e.g. methaemalbuminaemia) are under continued investigation.

Radiological

The BSG (1998) guidelines recommend that all patients predicted to have a severe attack by the above criteria should undergo a dynamic (intravenous contrast enhanced) CT scan between 3 and 10 days after admission. Areas of pancreatic necrosis demonstrate failure to enhance with intravenous contrast reflecting hypoperfusion (*Figures 2* and *3*). Also peripancreatic and intra-abdominal fluid collections can be assessed, allowing a CT-based grading of severity (*Table 5*). CT reliably predicts need for surgical intervention.

AETIOLOGY ASSESSMENT

Determining the aetiology of an attack of acute pancreatitis influences further therapeutic options and repeated investigation may aid this determination. The BSG (1998) guidelines suggest that only 25% of cases are idiopathic.

Clinical

An accurate alcohol history is important and evidence of prodrome suggesting viral cause. Medical and surgical conditions, any recent surgery, and medications should be recorded.

Biochemical

Gall-stones are suggested by a raised bilirubin or serum aminotransferase level, or both. Calcium and fasting lipids should be measured after the acute attack has settled.

TABLE 2.
Glasgow scoring system for predicting severity in acute pancreatitis

Age	>55 years
White blood cell count	>15x10^9/litre
Glucose	>10 mmol/litre
Urea	>16 mmol/litre
Arterial partial pressure of oxygen	<60 mmHg
Calcium	<2 mmol/litre
Albumin	<32 g/litre
Lactate dehydrogenase	>600 units/litre
Aspartate/alanine aminotransferase	>100 units/litre

TABLE 3.
Ranson's criteria for predicting severity in acute pancreatitis

Present on admission	Age	>55 years
	White blood cell count	>16 000/ul
	Blood glucose	>200 mg/dl
	Serum lactate dehydrogenase	>350 IU/litre
	Serum glutamic oxaloqcetic transaminase (aspartate aminotransferase)	>250 IU/litre
Developing during the first 48 hours	Haematocrit fall	>10%
	Blood urea nitrogen increase	>8 mg/dl
	Serum calcium	<8 mg/dl
	Arterial oxygen saturation	<60 mmHg
	Base deficit	>4 meq/litre
	Estimated fluid sequestration	>600 ml

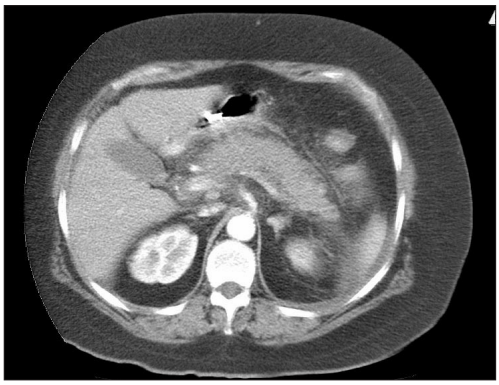

Figure 2. Early pancreatitis: pancreas enhancing, no necrosis.

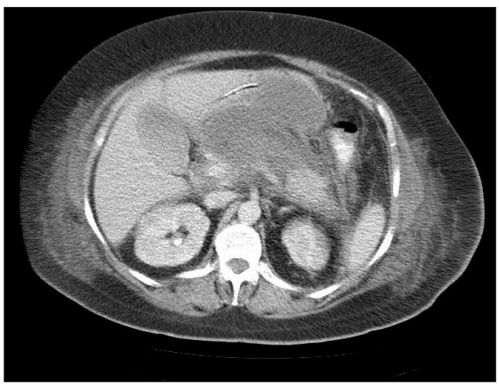

Figure 3. Same patient as Figure 2 with pancreatic necrosis, non-enhancement of body of pancreas.

Imaging

Ultrasound should be performed early in an attack to identify gall-stones and to size the common bile duct. This test should be repeated if negative.

Endoscopic retrograde cholangiopancreatography (ERCP) is recommended in the acute setting in the presence of jaundice or a dilated common bile duct (vide infra), and as an elective investigation in recurrent attacks to delineate anatomical variations, e.g. pancreas divisum.

CT is useful in obscure cases to rule out a pancreatic tumour and can be supplemented by magnetic resonance imaging if any doubt remains.

Endoscopic ultrasound may detect common bile duct stones. Bile sampling may reveal microlithiasis in recurrent cases. Sphincter of Oddi manometry and magnetic resonance cholangiopancreatography (MRCP) are under assessment.

MANAGEMENT

Management of mild acute pancreatitis

Around 80% of attacks are predicted to be mild, only 5% of deaths occur in this group and they usually have an unremarkable course. They can be managed on a general ward with monitoring to detect complications. Peripheral intravenous

TABLE 4.
APACHE II scoring system

	Acute physiology score								
	High normal range					Low normal range			
Variable	**4**	**3**	**2**	**1**	**0**	**1**	**2**	**3**	**4**
Temperature (°C)	>41	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	<29.9
Mean arterial pressure (mmHg)	>160	130–159	110–129		70–109		50–69		<49
Heart rate (ventricular; beats/min)	>180	140–179	110–139		70–109		55–69	40–54	<39
Respiratory rate	>50	35–49		25-34	12–24	10–11	6–9		<5
Oxygenation (mmHg)									
$AaDO_2$ when FiO_2 >0.5	>500	350–499	200–349		<200				
PaO_2 when FiO_2 <0.5					PO_2 >70	PO_2 61–70		PO_2 55–60	PO_2 <55
Arterial pH	>7.7	7.6–7.69		7.5–7.59	7.33–7.49		7.25–7.32	7.15-7.24	<7.15
Serum Na (mmol/litre)	>180	160–179	155-159	150–154	130–149		120–129	11-119	<110
Serum K (mmol/litre)	>7	6–6.9		5.5–5.9	3.5–5.4	3–3.4	2.5–2.9		<2.5
Serum creatinine (mg/100 ml)*	>3.5	2–3.4	1.5–1.9		0.6–1.4		<0.6		
Packed cell volume (%)	>60		50–59.9	46–49.9	30–45.9		20–29.9		<20
While blood cell count ($x10^3/mm^3$)	>40		20–39.9	15–19.9	3–14.9		1–2.9		<1
Glasgow coma scale (15 – score)									

The APACHE II score is given by the sum of the acute physiology score, the age (in years) points, and the chronic health points. Age points are assigned as follows: 0= <44; 2= 45–54; 3= 55–64; 5= 65–74; and 6=>75. Chronic health points are assigned if the patient has a history of severe organ system insufficiency or is immunocompromised, as follows: 5=non-operative or emergency postoperative patients; 2= elective postoperative patients. Organ insufficiency or an immunocompromised state must have been evident before admission to hospital and must conform to the following criteria: liver= biopsy confirmed cirrhosis and documented portal hypertension, episodes of past upper gastrointestinal bleeding attributed to portal hypertension, or prior episodes of hepatic failure/encephalopathy/coma; cardiovascular= New York Heart Association class IV (i.e. symptoms of angina or cardiac insufficiency at rest or during minimal exertion); respiratory= chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e. unable to climb stairs or perform household duties, or documented chronic hypoxia, hypercapnia, secondary polycythaemia, severe pulmonary hypertension (>40 mmHg), or respirator dependency; renal=receiving chronic dialysis; immunocompromised= the patient has received treatment that suppresses resistance to infection, e.g. immunosuppression, chemotherapy, radiotherapy, long term, high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g. leukaemia, lymphoma or acquired immunodeficiency syndrome. $AaDO_2$= alveolar–arterial oxygen difference; ARF= acute renal failure; FiO_2= fraction of inspired oxygen; PaO_2= arterial partial pressure of oxygen. *Double score for ARF

fluids are required and oral intake is traditionally withheld but a nasogastric tube is only needed for severe vomiting. Urinary catheterization is normally unnecessary. Pain is usually controlled with pethidine. Antibiotics are used only if specific infections occur. No specific treatment is of proven benefit and neither is CT scanning. With resolution of pain, observations and blood tests, oral fluids and then diet can be recommenced. Where acute pancreatitis is caused by gall-stones, common bile duct clearance and cholecystectomy is recommended when the patient recovers, preferably during the same hospital admission.

Management of severe acute pancreatitis

About 20% of cases of acute pancreatitis are severe and 95% of deaths occur in this group. The BSG (1998) guidelines aim for a mortality rate of less than 30%. One third of deaths occur in the first week from multiple organ failure and most of the rest result from infected pancreatic necrosis. BSG guidelines recommend management in an intensive care unit or high dependency unit. Dynamic CT (*Figures 2* and *3*) should be performed between days 3–10 after admission and prophylactic intravenous antibiotics should be used in all cases (see below). Nutritional support is achieved with a nasoenteral feeding tube radiologically placed beyond the ligament of Trietz in the absence of an ileus. This is cheaper and has fewer complications than total parenteral nutrition. In cases caused by gall-stones the BSG guidelines recommend urgent ERCP and sphincterotomy when there is no response to treatment within 48 hours. These guidelines also discuss caring for patients with severe disease in specialized units where multidisciplinary expertise is available on site. Full intensive care facilities, emergency ERCP and expert radiology input should be available and supervised by a surgeon with pancreatico-biliary expertise.

SYSTEMIC COMPLICATIONS

Respiratory: Pulmonary oedema, pleural effusions, consolidation, respiratory distress syndrome (*Figure 1*).

Cardiovascular: Hypovolaemia as a result of capillary leak, high output and low resistance shock, intra-abdominal haemorrhage.

Renal: Acute renal failure and need for renal replacement therapy.

Haematological: Disseminated intravascular coagulopathy.

Metabolic: Hypocalcaemia, hypomagnesaemia, hyperglycaemia.

Gastrointestinal: Gastrointestinal haemorrhage, ileus.

Miscellaneous: Confusion, delirium tremens, possibly impaired defence against infection.

LOCAL COMPLICATIONS

Acute fluid collections: These occur early in the course of acute pancreatitis, are located in or near the pancreas, and always lack a wall of granulation or fibrous tissue. Most resolve spontaneously and are not life threatening.

Pancreatic necrosis: Pancreatic necrosis (*Figure 3*) is a diffuse or focal area(s) of non-viable pancreatic parenchyma, which is typically associated with peripancreatic fat necrosis. The onset of infection results in infected necrosis, which is associated with a trebling of the mortality risk.

A rising CRP level suggests necrosis and the gold standard is radiological diagnosis using dynamic CT, 3–10 days after admission. Magnetic resonance imaging is under evaluation.

Infection occurs in 30–70% of patients with necrosis; selective gut decontamination using enteral antibiotics or intravenous antibiotics reduces this incidence (Baron and Morgan, 1999). Care must be taken with invasive procedures, especially central lines where aseptic technique is essential. Intravenous cefuroxime or imipenem is recommended as prophylaxis in all cases of severe acute pancreatitis and some also recommend use of fluconazole. Fever, leucocytosis and abdominal pain occur in both sterile and infected necrosis. Bacteriological status may be determined by CT-guided fine needle aspiration and evaluation with microscopy and culture. It is indicated where the condition deteriorates or fails to improve with aggressive supportive care.

Intervention in sterile necrosis is of unproven benefit, but infected necrosis is considered uniformly fatal without intervention. Aggressive surgical pancreatic debridement (necrosectomy) is the standard of care. Demarcation between viable and necrotic tissue improves with time, but infection needs prompt action.

The conventional approach to surgical debridement involves necrosectomy with place-

TABLE 5.
Contrast enhanced computed tomography grading system

Grade	Computed tomography morphology
A	Normal
B	Focal or diffuse gland enlargement; small intrapancreatic fluid collection
C	Any of the above plus peripancreatic inflammatory changes and <30% gland necrosis
D	Any of the above plus single extrapancreatic fluid collection and 30–50% gland necrosis
E	Any of the above plus extensive extrapancreatic fluid collection, pancreatic abscess and >50% gland necrosis

ment of drains and reoperation as required based on clinical and radiological follow up. Open or semi-open management involves necrosectomy and scheduled repeated laparotomy or open packing leaving the abdominal wound exposed. Closed management involves necrosectomy with extensive lavage and closure of the abdomen over large bore drains for continuous high volume postoperative irrigation. Mortality is 20% and pancreatic or gastrointestinal fistulas occur in up to 40% often requiring further surgery.

There are a few alternative methods of debridement. Percutaneous therapy (radiological) involves irrigation and drainage through large bore catheters. Endoscopic drainage and laparoscopic debridement are under evaluation. Experience with these non-surgical procedures is limited and they should only be performed by experts.

Pancreatic abscess: This is a circumscribed intra-abdominal collection of pus, usually in proximity to the pancreas, containing little or no pancreatic necrosis, which arises as a consequence of acute pancreatitis. These present up to several months after an acute attack and require radiological or surgical treatment.

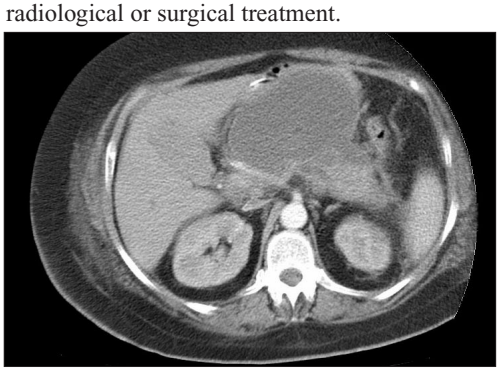

Figure 4. Same patient as Figures 2 and 3 with pseudocyst forming.

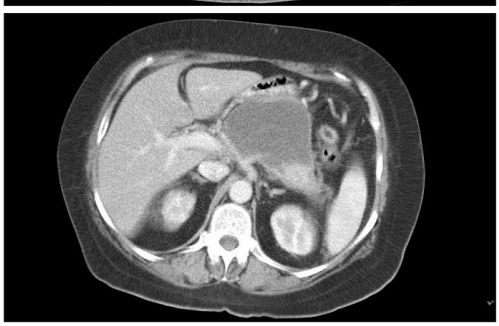

Figure 5. Same patient with mature pseudocyst.

KEY POINTS

- Acute pancreatitis is common and potentially lethal.
- Early identification of severe pancreatitis is possible.
- Intensive monitoring and system support are key.
- Aggressive imaging identifies potentially remediable complications.
- Minimally invasive interventions have largely replaced open surgery.
- Severe acute pancreatitis should by managed with a multidisciplinary approach, ideally in a specialized centre.

Acute pseudocyst: An acute pseudocyst (*Figures 4* and *5*) is pancreatic juice enclosed in a wall of fibrous or granulation tissue that arises following an attack of acute pancreatitis. Formation of a pseudocyst takes about 4 weeks. These are detected by imaging or present as a palpable mass, gastric outlet or biliary obstruction. Complications include rupture and pseudoaneurysmal haemorrhage. MRCP or ERCP can show communication with the pancreatic duct or obstruction. Percutaneous and endoscopic treatments are available but there is a risk of haemorrhage. Surgical options include cystogastrostomy which fashions a 5 cm stoma through the posterior gastric wall, cystojejunostomy or cystoduodenostomy. A pseudocyst of the tail may require distal pancreatectomy.

LONG-TERM SEQUELAE

These depend on the severity of necrosis, degree of debridement, and alcohol as a cause and its continued abuse. Exocrine studies may show insufficiency in most patients up to 2 years after severe acute pancreatitis but use of pancreatic enzymes should be restricted to those with steatorrhoea and weight loss. Subtle glucose intolerance is common but overt diabetes mellitus is uncommon. Persistent abdominal pain and acute recurrent pancreatitis may be investigated with pancreatography.

Future medical treatment

Some recent and ongoing clinical trials are investigating the role of anticytokines in treating acute pancreatitis, e.g. platelet-activating antagonists. Octreotide (a somatostatin analogue) and plasma exchange therapy are also under evaluation.

CONCLUSIONS

Acute pancreatitis is an important, evolving surgical condition. Modern management involves a multidisciplinary approach with supportive care and aggressive diagnostic imaging to identify remediable complications promptly. The role of operative intervention is limited and future advances may involve molecular therapies. HM

Conflict of interest: none.

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