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WORKING PARTY REPORT

Guidelines for the management of acute pancreatitis

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INTRODUCTION

Acute pancreatitis (AP) is a common disease that normally runs a benign course in the majority of patients. However in up to 20% of individuals the disease is severe and may be associated with a mortality close to 20%.[1,2] Over the last 5 years a number of developments in the management of pancreatitis have evolved and these developments are having an impact in the treatment of patients, lowering the morbidity and mortality.

The aim of this working party report is to incorporate the new developments in the treatment of pancreatitis into recommendations and guidelines for practice. The working party was formed under the auspices of the program committee of the Bangkok World Congress of Gastroenterology 2002. Following an invitation from the chair, members of the committee first met in Chicago in late 2000 to define the outline of the report and the parameters that would be considered. The committee was allocated tasks and these were fulfilled, culminating in a draft document that was produced in time for meeting in Atlanta in May 2001 for a 2-day working meeting. Prior to this meeting the draft document was reviewed, the statements of fact checked by reviewing published manuscripts relevant to the recommendations made. The search strategy was Medline based. However, in addition, the reference sources of the members of the working party were used and the members were asked to reference all of their recommendations.

At the Atlanta meeting the draft document was reviewed and the recommendations plus guidelines agreed upon. Following this, the members again revised the second draft of the document based on the agreed recommendations. The document was then rescrutinized and the guidelines were allocated the corresponding level of evidence as determined from currently published studies.

The following classification of levels of evidence has been used in the summary of the document.[3]

Level 1: Evidence obtained from systematic reviews of all relevant randomized controlled trials.

Level 2: Evidence derived from at least one properly designed randomized controlled trial.

Level 3: Evidence from a well-designed control trial without randomization; or from well-designed cohort or case–control analytical studies; preferably from more than one center or research group; or from multiple time series with or without intervention.

Level 4: Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees. This level signifies the need for further research.

The final document was prepared and submitted to the Secretary General of OMGE for final scrutiny prior to publication for the World Congress of Gastroenterology.

At the congress the recommendations were presented and questions and comments noted. These comments were incorporated into the final guidelines where appropriate.

Terminology and definitions

The 1992 Atlanta International Symposium on Acute Pancreatitis put forth a classification system of acute pancreatitis with the intent of providing clinical guidance and an exact vocabulary across institutions and within the literature.[4] The definitions are summarized in the (Table 1).

Epidemiology of acute pancreatitis

The incidence of acute pancreatitis is difficult to ascertain in the community. All incidence rates of acute pancreatitis are based on hospital data and their accuracy is heavily influenced by the method of data collection.

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Estimated incidences range from 5.4/100 000 population per year in England to 79.8/100 000 in the USA (Table 2).[5,6] In countries where data have been collected there appears to be an increase in the incidence of acute pancreatitis.[7] In Scotland, the incidence was 9.4/100 000 in 1968–80 but it rose to 31.8 in 1985–95.[8] Similar increases have been noted in England,[9] Denmark,[10] Sweden,[11] Finland,[12] Germany[14] and the Netherlands.[13] This rise in incidence has been attributed to increased alcohol consumption in Finland and the Netherlands, but may well reflect improved diagnostic capability during this period. Some patients with acute biliary pancreatitis who might have been missed earlier are now being diagnosed with the use of endoscopic ultrasonography, contrast-enhanced computed tomography and biliary microlith examination. One important finding in the Swedish study was that the relapse rates over a period of 10 years varied according to the etiology of pancreatitis.[11] It was 48% for alcoholic pancreatitis, 21% for gallstone pancreatitis, 18% for idiopathic pancreatitis and 5–7% for other etiologies (overall 28.7%). The magnitude of the problem of acute pancreatitis is evident from these figures, despite concerns of applicability of the figures to other regions with different sociocultural and economic milieu.

Table 1 Definitions

Term	Definition
Acute pancreatitis	Acute inflammation of the pancreas
Mild acute pancreatitis	Minimal organ dysfunction responsive to fluid administration
Severe acute pancreatitis	*One of the following:*
	Local complications (pancreatic necrosis, pancreatic pseudocyst, pancreatic abscess)
	Organ failure
	≥ 3 Ranson criteria
	≥ 8 APACHE II points
Acute fluid collections	Fluid collection in or near the pancreas
	Occurs early in course
	Lack a defined wall
Pancreatic necrosis	Non-viable pancreatic tissue
	Diagnosis by i.v. contrast-enhanced CT scan
Acute pseudocyst	Fluid collection containing pancreatic secretions
	Defined wall
Pancreatic abscess	Collection of pus
	Usually in or near pancreas

No seasonal or weekly pattern of acute pancreatitis has been observed.[14] Men are affected much more than women and the main age group affected is 40–60 year olds.[15] The reasons for the male preponderance is probably the higher incidence of alcoholic pancreatitis and also because gallstone pancreatitis is usually seen equally in both males and females despite a higher prevalence of gallstones in females as compared with that in males.

The mortality from acute pancreatitis in the general population has been estimated to be 1.3/100 000 population in Sweden, 0.9–1.6/100 000 population in England and 1.3/100 000 in Scotland.[8,9,11] Most patients develop a mild form of acute pancreatitis and survive the illness. However, about 20–30% of patients develop pancreatic necrosis and 25% develop severe life-threatening complications.[16,17] These patients are at a high risk of death and the mortality may be as high as 30%.[16] The overall mortality in hospitalized patients is around 10% although reported figures vary from 2% to 22%. In older patients the mortality is much higher (15–25%) than in younger patients (< 10%). In a multicenter audit, deaths from acute pancreatitis were found to be 9% in a study of 631 patients from nine centers in the UK.[18]

Table 2 Overall incidence of acute pancreatitis in different parts of the world*

Authors	Region	Period	Incidence: (per 100 000/year)
Trapnell and Duncan[5]	Bristol	1961–67	5.4
Corfield *et al.*[9]	Bristol	1968–79	7.3
Tran and Schilfgaarde[13]	Netherlands	1971	6.5
Assmus *et al.*[14]	Germany	1989–94	15.6
Worning[10]	Denmark	1981	26.8
		1990	35.4
Go[6]	USA	1987	49.5
			79.8
Jaakkola and Nordback[12]	Finland	1970	46.6
		1989	73.4
McKay *et al.*[8]	Scotland	1985	25.8
		1995	41.9

*Modified from Lankisch.[7]

Etiology of acute pancreatitis

There are varied etiologies of acute pancreatitis (Table 3), the commonest being gallstones. Table 4 provides the relative percentage of these etiologies in different geographical regions.[11,19,20] Some of the important etiologies are discussed below.

Gallstones

Gallstones continue to be the leading cause of acute pancreatitis in most series (30–60%). Microlithiasis (occult gallstones) is a well-known cause of acute pancreatitis. In the absence of gallstones and other recognizable causes of acute pancreatitis, every effort should be made to diagnose microlithiasis before labeling a patient as having idiopathic pancreatitis. Biliary microscopy and endosonography are the recommended tests to diagnose microlithiasis.[21,22] Biliary sludge is diagnosed by conventional abdominal ultrasonography and this term has been used interchangeably with microlithiasis in the context of etiology of acute pancreatitis. Since occult gallstones have been known of, the percentage of patients with idiopathic pancreatitis has substantially reduced. Many studies have shown that microlithiasis is the cause of presumed idiopathic acute pancreatitis in 50–73% of patients.[23–25] Recurrent attacks of pancreatitis may continue even after cholecystectomy in some patients with microlithiasis.

Table 3 Various etiologies of acute pancreatitis

Common causes:
Gallstones (including microlithiasis)
Alcohol
Idiopathic
Hyperlipidemia
Hypercalcemia
Sphincter of Oddi dysfunction
Drugs and toxins
Post-endoscopic retrograde cholangiopancreatography
Traumatic
Postoperative
Uncommon causes:
Pancreas divisum
Periampullary cancer
Cancer of the pancreas
Periampullary diverticulum
Vasculitis
Rare causes:
Infective: Coxsackie virus, mumps, HIV, parasitic. Ascariasis
Autoimmune: systemic lupus erythematosus, Sjogren's syndrome
α-1 antitrypsin deficiency

Table 4 Comparative etiologies of acute pancreatitis at various centers

Aetiology	New York, USA[19]	Sweden[11]	New Delhi, India[20]
Gallstones	32%	38.4%	49%
Alcohol	20%	31.8%	23.6%
Idiopathic	18%	23.2%	16.5%
Miscellaneous	29%	6.6%	10%

Alcohol

Alcohol is the second commonest cause overall,[19] although in a few studies it has been reported as the predominant cause.[26] It is responsible for about 30% of all cases of acute pancreatitis. The main controversy regarding alcohol-related pancreatitis is whether the acute episodes of pancreatitis in alcohol abusers represent exacerbations of chronic pancreatitis or are truly recurrent attacks of acute pancreatitis. Most series on the etiology of acute pancreatitis, however, include alcohol as an important etiological factor. The proponents of the necrosis-fibrosis hypothesis, indeed, believe that repeated attacks of acute alcoholic pancreatitis lead to chronic pancreatitis.[26] There are major unanswered questions about alcoholic pancreatitis. Why do only a minority of alcoholics develop pancreatitis? Are there cofactors in the causation of alcoholic pancreatitis? What is the exact mechanism of pancreatic injury in alcoholic pancreatitis? Is alcohol a direct toxin or is the injury mediated through some other process such as over-stimulation or over-sensitization of acini to cholecystokinin?[27]

Hyperlipidemia

Hyperlipidemia is the cause of acute pancreatitis in about 1.3–3.8% of cases.[28] It is hyperlipidemia type 1, 4 or 5 that causes pancreatitis and is generally associated with serum triglyceride levels >1000 mg/dL. Patients with diabetes or those on certain drugs may have high triglyceride levels causing pancreatitis. Many alcoholics, however, have very high levels of triglycerides, which may confuse the picture with regard to the actual cause of pancreatitis.

Hyperparathyroidism

Hyperparathyroidism is a rare cause of pancreatitis and 8–19% of all patients with hyperparathyroidism may develop acute pancreatitis.[29,30] Similarly, other conditions causing hypercalcemia such as metastatic bone disease, vitamin D poisoning and sarcoidosis may rarely cause acute pancreatitis.

Structural abnormalities

Structural abnormalities that may be responsible for acute pancreatitis include bile duct lesions such as choledochal cyst, sclerosing cholangitis, primary bile duct stones, abnormal pancreatic-biliary junction, and pancreatic duct anomalies such as pancreas divisum, ampullary or pancreatic cancer, and others like duodenal diverticula, and sphincter of Oddi dysfunction

(SOD). Sphincter of Oddi dysfunction needs additional mention as it has been suggested to be the cause of acute idiopathic pancreatitis in 15–57% of cases.[31,32] Elevated pressure of the main pancreatic duct, delayed drainage of contrast and a dilated pancreatic duct are features suggestive of SOD. It has been shown that surgical sphincteroplasty with pancreatic duct septoplasty alleviates further attacks of pancreatitis.[33] However, the role of endoscopic sphincteroplasty (ES) and sphincterotomy is still under investigation.

Post-endoscopic retrograde cholangiopancreatography pancreatitis

Acute pancreatitis may occur in 1–10% of patients following endoscopic retrograde cholangiopancreatography (ERCP).[34,35] Asymptomatic raised serum amylase is seen in about 50% of patients. Similarly, sphincter of Oddi (SO) manometry is associated with a high risk of pancreatitis.

HIV and acute pancreatitis

In a recent study, 14% of patients with HIV infection developed acute pancreatitis over a period of 1 year. The factors associated with the development of acute pancreatitis were gallstones, intravenous drug use, pentamidine intake, *Pneumocystis carinii* and *Mycobacterium avium-intracellulare* infections, and CD count of < 500 cell/mm^3.[36]

Traumatic pancreatitis

Abdominal trauma even if mild, blunt or sharp, may result in acute pancreatitis. Similarly, acute pancreatitis may follow abdominal operations.

Idiopathic acute pancreatitis

About 10% of patients are left with no identifiable cause despite a thorough biochemical, ultrasonographic and endoscopic examination.[37,38] Rare causes such as infectious pancreatitis, autoimmune pancreatitis, ischemic pancreatitis and pancreas divisum should be considered in such patients and accordingly investigated.

For determining the etiology of acute pancreatitis, investigations divided into four phases have been suggested (Table 5).[19,39] Phase I investigations should be done after a single episode of acute pancreatitis. The level of investigations should increase if there are recurrent attacks of pancreatitis and no obvious cause is identified.

Table 5 Suggested plan of investigative work up of patients with acute pancreatitis*

Detailed history: including family history, alcohol intake, drug intake, tropical residence
Phase 1:
Serum biochemistry: amylase, lipase, liver function tests, lipids, calcium
Abdominal ultrasound
CT scan
Phase 2:
Endoscopic retrograde cholangiopancreatography /MRCP
Bile examination for biliary crystals
Endoscopic ultrasound
Sphincter of Oddi manometry
Phase 3:
Viral studies α-1 antitrypsin activity, autoimmune markers
Pancreatic and biliary cytology
Secretin stimulation test for pancreatic function test to rule out chronic pancreatitis
Investigational:
Genetic studies: Cationic trypsinogen gene mutation, CFTR mutation, SPINK 1 mutation

*Modified from references 19 and 39.

MRCP, magnetic resonance cholangiopancreatography; CFTR, cystic fibrosis transmembrane condnctance regulator; SPINK 1, serine protease inhibitor Kazal type 1.

Clinical presentation

The cardinal symptom of acute pancreatitis is abdominal pain. Most patients present with an acute onset of upper abdominal pain usually located in the epigastrium. The pain is moderate to severe in the vast majority of patients but may be mild. It increases in severity for the first few hours and then plateaus and lasts for several hours to days. The pain radiates to the back quite commonly owing to the retroperitoneal location of the pancreas. It may also radiate to the flanks, chest, shoulders and lower abdomen. The character of the pain is steady and boring, but not colicky. The pain may be very severe and may not respond even to narcotic analgesics. In some patients the pain may become less on bending forward and drawing the knees upwards. In patients with mild pancreatitis the pain usually abates and does not recur. In severe pancreatitis the pain may continue for days and may become generalized if peritonitis develops. Development of large acute fluid collection or pseudocyst later in the course of illness may be associated with continuation or recurrence of pain.

Painless pancreatitis, although uncommon, is a definite and well-recognized entity. It is seen in the setting of peritoneal dialysis, postoperative situations, especially renal transplantation, Legionnaire's disease, and in some cases may present as subcutaneous fat necrosis (panniculitis).[40–42] In fact, up to 12–42% of patients with acute pancreatitis are diagnosed only at postmortem examination.[18,43,44]

Nausea and vomiting are other common symptoms of acute pancreatitis. Some patients develop localized or generalized paralytic ileus, which may cause abdominal distension and vomiting.

Fever is an important sign in patients with acute pancreatitis.[45] Most patients develop fever in the beginning of the illness that may go up to 102°F (39°C) and last for a few days. The timing of fever is very important in determining its cause and significance. Fever in the first week of acute pancreatitis is due to acute inflammation

and is mediated by inflammatory cytokines.[46] This fever subsides with 'cooling off' of the pancreatic inflammation. Fever in the second or third week in patients with acute necrotizing pancreatitis is usually due to infection of the necrotic tissue and is much more significant. Infected necrosis carries a high mortality and warrants surgical intervention.[47]

Fever may be due to acute cholangitis in patients with gallstone-induced acute pancreatitis and mandates prompt biliary decompression. Thus, it is important to determine the likely cause of fever in a patient with acute pancreatitis because that will guide further management of that patient. In a prospective study, the causes of fever as well as the timing of fever were studied. Fever occurred in 60% of patients with acute pancreatitis; in 22% the fever was due to pancreatitis per se, in another 33% it was due to extra pancreatic infections (including cholangitis) and in about 45% it was due to infected pancreatic necrosis.[48] In another prospective study of 169 patients with acute pancreatitis, it was found that a total of 63 patients (37%) were documented to have infections at various sites.[20] The infection in patients with acute pancreatitis is usually due to Gram-negative bacteria (Table 6), but the routine use of antibiotics in severe acute pancreatitis has altered the common infections.[49–52]

A patient with acute pancreatitis appears in obvious distress. Cardiovascular system abnormalities may include tachycardia and hypotension due to hypovolemia or vasodilation and initial systemic inflammatory response syndrome (SIRS). The chest findings may reflect the presence of atelectasis, with basal crepitations, or the presence of a pleural effusion especially on the left side. In one study, pleural effusion was found to be associated with severe pancreatitis and a bad prognosis.[53] Patients with acute pancreatitis may be dyspneic and may go into respiratory failure. They may develop delirium, confusion and rarely may become comatose. Neurological manifestations are due to hypoxia, electrolyte imbalance, hypotension, alcohol withdrawal or toxemia. Purtscher's retinopathy is a rare complication due to posterior retinal artery block; the patient presents with a sudden loss of vision and cotton wool appearance and exudates on the fundus.[54] Patients with acute pancreatitis may develop oliguria and go into acute renal failure. Features of acute renal failure in the form of fluid overload, acidosis and electrolyte imbalance may supervene. Abdominal signs are usually less marked compared with the severity of pain; that is, only mild tenderness is present in the face of severe pain. In patients with severe pancreatitis, signs of peritonitis may supervene with generalized tenderness and rigidity. Bowel sounds are generally absent or sluggish. Ascites is due to chemical peritonitis and exudation of fluid from the inflamed pancreatic bed. Pancreatic ascites may occur due to disruption of the main pancreatic duct but is rare following acute pancreatitis. Grey-Turner's sign is blue-gray discoloration of abdominal flanks due to exudation of blood-stained fluid into the subcutaneous tissue, usually 72 h into the illness. A bluish discoloration in the periumbilical area may occur in patients with severe pancreatitis and is known as Cullen's sign. Some patients may develop left-sided portal hypertension due to splenic vein thrombosis and present with splenomegaly and fundal variceal bleeding. Necrosis of the transverse colon in severe pancreatitis is a lethal complication and the patient presents with severe peritonitis.[55] Acute fluid collections and pseudocysts may give rise to palpable lumps in the abdomen.

Diagnosis: Biochemical

The diagnostic process of acute pancreatitis (AP) is based on the clinician's index of suspicion; clinical history and physical examination determining the so-called pretest probability of disease.

Whenever acute upper abdominal pain is combined with elevated pancreatic enzyme levels the final diagnosis will be fully established by imaging and/or the manner in which the clinical course of disease unfolds.

The biochemical tests are useful both for excluding or ascertaining AP; many single parameters or multiple score systems have been advocated in the assessment of severity as stressed in the next section.

The pre and the post-test probability of acute pancreatitis

Clinicians express the pretest probability (index of suspicion) with terms such as 'probable, possible and unlikely'. The role of the diagnostic test is to change the pretest into a post-test probability of 0% if negative and 100% if positive. Unfortunately, an ideal test does

Table 6 Microorganisms isolated from patients with acute pancreatitis and infections

Authors	Pancreatic complication	Mono-microbial infection (%)	Poly-microbial infection (%)	Gram negative			Gram positive		Anerobic
				E. coli (%)	*Pseudo-monas*	*Entero-bacter*	Staphylo-cocci (%)	Entero-cocci (%)	
Beger *et al.*[49]	Infected necrosis	–	–	53	11	56	11	3	11
Gerzof *et al.*[51]	Pancreatic infection	–	–	24	5	45	12	24	7
Fedorak *et al.*[50]	Infected necrosis	43	57	24	14	34	57	33	9
Bradley[52]	Pancreatic infection	53	47	47	10	14	2	3	–
Garg *et al.*[20]	Infected necrosis	68	32	25	27	5.5	8	6	–

not exist. Therefore, the clinical impact of the biochemical test is its ability to change the pretest probability into a higher one if positive and into a lower one if negative.

The post-test probability is certainly related to the sensitivity (probability of a positive test in the presence of the disease) and specificity (probability of a negative test in the absence of the disease) but also, and in the same magnitude, by the pretest probability; as a consequence, tests with a limited sensitivity and specificity in experienced hands may result in a post-test probability equal or superior to the one achieved with more accurate tests used by inexperienced clinicians.[56]

Two studies carried out in autopsy series[43,44] show that about 40% of the deaths due to AP are undiagnosed in life and that the majority of these patients did not have abdominal pain at the time of hospitalization. In order to improve the possibility of the pretest probability it is important to consider the diagnosis of AP also in cases of shock of unknown origin, during the postoperative period after major surgery and in severely unwell patients.

Serum pancreatic enzymes

Serum pancreatic enzyme measurement is the 'gold standard' for the diagnosis of AP. Which test is the best? The majority of the studies on this topic are already carried out in 'high-index of suspicion' populations suffering from abdominal pain. The discharge diagnosis is often used as the definitive diagnosis of AP, but pancreatic enzymes tests influence this final diagnosis. As a consequence, the final judgment regarding the accuracy of the tests is probably overestimated.[56]

Amylase, lipase, elastase and trypsin are released into the bloodstream at the same time but the clearance varies with different sensitivities depending on the timing of blood sampling from the onset of disease, affecting the sensitivity of the test. For example, the sensitivity of pancreatic amylase between the second and the fourth day decreases below 30%, whereas lipase or elastase still has sensitivity higher than 80%. An important concept arises from this: the diagnosis of AP should not rely on arbitrary limits of values three or four times greater than normal, but values interpreted in light of the onset of abdominal pain.[56]

Despite a huge number of papers dealing with the enzymatic diagnosis of AP, only a few include consecutive patients with abdominal pain studied as a population in an effort to prospectively analyze the accuracy of serum pancreatic enzymes.[57–64] A recent in-depth review[56] suggests that the total amylase has a sensitivity of 83%, the P-amylase of 94% and the lipase of 92%.

Because of the frequent hyperamylasemia found in several extrapancreatic diseases, it is not surprising to find a significant lower specificity for total amylase versus the P-amylase and lipase (88% versus 93% versus 96%, respectively).

Many other proenzymes and active enzymes have been evaluated in recent years. These include trypsinogen, elastase-1, phospholipase, urinary trypsinogen-2, pancreatitis-associated protein, trypsin-antitrypsin complex and pancreatic specific protein, but their quantification (aside from urinary trypsinogen activation peptide [TAP]) is still not applicable in the emergency setting because of methodological limitations and/or costs.

In conclusion, the pretest probability of AP ranges widely from 7% to 60% with an average of 21%. In cases with elevated total amylase, a post-test probability of 65% is obtained and this figure rises up to 78% using P-amylase and to 86% by lipase. Moreover, the serum levels of lipase are elevated for a longer period when compared with total and P-amylase[65] making this the enzyme with higher diagnostic accuracy.[56]

Activation peptides

Among several activation peptides studied so far, the only one with significant clinical impact seems to be the above-mentioned TAP that was first described in 1990.[66] High levels of the activated peptide are found in urine from patients suffering from AP showing a correlation between severity of the disease and TAP levels. Moreover, urinary TAP correlates with C-reactive protein (CRP) and interleukin-6 (IL-6), but it is not present in mild AP after ERCP and peritoneal fluid levels are directly proportional to the amount of glandular necrosis.[62,67,68]

Serum markers

Serum markers cannot be solely considered as parameters useful in the diagnosis of AP, but also, as complementary data seem to suggest, they can elucidate the presence of necrosis and, as a consequence, the potential and/or real severity of the underlying disease.

Leukocyte migration and activation may represent the major determinant factor for both local (necrosis development) and systemic (multi-organ impairment and failure) complications.[69] Once activated, monocytes and macrophages release a number of cytokines, including IL-1, IL-8 and tumor necrosis factor (TNF). These mediators are the main inducers of hepatic synthesis of acute phase proteins such as the CRP. This implies that IL-6 and, in particular, IL-8, may be earlier indicators when compared with CRP.[70–72] The IL-6 and IL-8 increase precedes that of CRP by 24 h, while TNF does not change at all after a decrease at day two. High sensitivity and one and two while at day three CRP surpassed both of them.[71]

C-reactive protein remains the only generally used parameter today because it is readily available in every laboratory. Values over 150 mg/L after 72 h are closely related to necrotizing AP.[73] Recent technological progress has led to increased availability of test methods for both IL-6 and 8.

Severity assessment

The mortality of acute pancreatitis is dependent on a number of factors including the age and obesity of the

patient. Age over 70 and a body mass index in excess of 30 kg/m^2 greatly increase the risk. Those over 70 years have a 19% mortality.

Up to 50% of patients who die may do so within the first 7 days of illness from multi-organ dysfunction syndrome (MODS), formerly described as multiorgan failure (MOF). In most of these patients the SIRS predicts the persistence of organ dysfunction (OD) and is probably at least as accurate as multiple factorial grading systems such as APACHE II (Table 7)[74] the Glasgow (Table 8) or Ranson scoring systems.

It is important to recognize that organ dysfunction may be a transient phenomenon which improves in the initial resuscitation phase and that persistence, or deterioration of OD, are important predictors of severity. A proportion of patients have organ dysfunction at the time of admission to hospital, but in most this improves with simple resuscitation methods.

Table 7 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 b.p.m.)	> 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)									
*A*aDO_2 when *F*iO_2	> 500	350–499	200–349		< 200				
*P*aO_2 when FiO_2					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/L)	> 180	160–179	155–159	150–154	130–149		120–129	110–119	< 110
Serum K (mmol/L)	> 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		
Double score for ARF									
Packed cell volume (%)	> 60		50–59.9	46–49.9	30–45.9		20–29.9		< 20
White blood cell count (× 103/mm^3)	> 40		20–39.9	15–19.9	3–14.9		1–2.9		< 1
Glasgow coma scale*									

*Score = 15 – actual Glasgow coma scale.

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 polycythemia, severe pulmonary hypertension (> 40 mmHg), or respirator dependency; renal, receiving chronic dialysis; and 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, such as leukemia, lymphoma, AIDS. *A*aDO_2, alveolar–arterial oxygen difference; *P*aO_2, arterial partial pressure of oxygen; *F*iO_2, fraction of inspired oxygen; ARF, acute renal failure.

Table 8 Glasgow scoring system for the prediction of severity in acute pancreatitis

Arterial PaO_2	< 60 mmHg
Serum albumin	< 32 g/L
Serum calcium	< 2.0 mmol/L
White cell count	$> 15 \times 10^9$/L
AST	> 200 μ/L
LDH	> 600 IU/L
Blood glucose	> 10 mmol/L (non-diabetic)
Plasma urea	> 16 mmol/L

AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

The presence of a high APACHE II SCORE at admission (8 or greater), a pleural effusion, a high body mass index, evidence of necrosis on contrast-enhanced CT (CECT) and a CRP level greater than 150 mg/L at 48 h are all useful markers of severe disease.

The measurement of urinary TAP is now a commercial reality and early elevated levels are associated with more severe AP, such that this may well prove to be a useful practical addition to the early investigations performed in these patients.

More sophisticated markers (which are usually only available in retrospect) include IL-6 and IL-8 as well as polymorphonuclear elastase (PMN elastase) and phospholipase A2; all show potential for the future.

The greater the percentage of the pancreas that is necrotic, especially if it affects the head of the gland, the greater the likelihood of later infection. Infection of the necrotic tissue after the first week of illness is the major determinant of later outcome. However, it is organ failure in which respiratory failure dominates that determines outcome in the majority of difficult cases to manage.

Clinical assessment by an expert is as accurate in grading severity as any of the laboratory-based multifactorial systems, and in the absence of any proven pharmaceutical agent to improve prognosis the main purpose of such segregation of cases is the appropriate allocation of high dependency or intensive therapy beds, as well as potential allocation of some patients to early ES. These are the patients who, in addition to objective signs of severe AP, have imaging evidence and blood tests suggesting obstruction of the common bile duct (CBD).

Recommendations for severity assessment

Immediate assessment

Clinical assessment including great care to assess respiratory, cardiovascular and renal compromise.
Body mass index. There is considerable risk (> 30 kg/m^2) or much greater risk > 40 kg/m^2
Chest X-ray. Is there a pleural effusion present?
Contrast-enhanced CT. Is there more than 30% of the volume of the pancreas malperfused?
APACHE II score. Is it 8 or greater?
Presence of organ failure.

24 h assessment

Clinical assessment.
Glasgow score.
C-reactive protein > 150 mg/L.
Presence of organ failure.

48 h assessment

Clinical assessment.
Glasgow score.
C-reactive protein.
The presence of organ failure.

The role of imaging in the diagnosis and staging of acute pancreatitis

Dynamic contrast-enhanced CT (CECT) is the imaging modality of choice for diagnosis, staging, and detection of complications of acute pancreatitis. Other techniques, such as ultrasonography, ERCP, and angiography are useful for problem solving and for specific evaluation of the pancreatic and biliary ducts and vascular system when involvement is known to be present and more precise anatomical information is required.

Contrast-enhanced CT has three major roles in evaluation of patients with known or suspected acute pancreatitis: (i) diagnosis; (ii) staging of the severity of the inflammatory process; and (iii) detection of complications, particularly the identification and quantification of parenchymal and peripancreatic necrosis.

Diagnosis

Contrast-enhanced CT currently is the most accurate single imaging modality for diagnosis, staging the severity of the inflammatory process, and detecting complications of acute pancreatitis.[75–79] Most importantly, CECT has been shown to have a sensitivity of 87% and an overall detection rate of over 90% for pancreatic gland necrosis.[76,80,81] The CT findings of acute pancreatitis depend upon the severity of the disease and are discussed below for each of the stages.

Staging

The ability to stage accurately the severity of acute pancreatitis may have important prognostic and treatment implications.[76,82,83] The morphological severity of acute pancreatitis can be defined precisely using the CT Severity Index (CTSI) developed by Balthazar and coworkers (Table 9).[76]

First, the severity of the acute inflammatory process is categorized into stage A through E, corresponding to scores of 0–4, respectively.

Table 9 Acute pancreatitis grade and CT severity index (CTSI)

CT grade	Score
A	0
B	1
C	2
D	3
E	4
Add to CT score the necrosis score	
Necrosis	Score
None	0
One-third	2
One-half	4
> One-half	6
CTSI = CT grade score + necrosis score (0–10)	

Modified from: Balthazar EJ *et al. Radiology* 1990; 174: 331–336.

Table 10 CT Severity index

Index	Morbidity	Mortality
0–3	8%	3%
4–6	35%	6%
7–10	92%	17%

Modified from: Balthazar EJ *et al*. Radiology 1990; 174: 331–336.

Stage A: Normal pancreas (score 0). Patients with acute edematous or interstitial pancreatitis may have a normal pancreatic CT in 20–25% of cases. This is because the inflammatory process is so mild that no peri- or intrapancreatic fluid collections form and no changes occur in the peripancreatic soft tissues. The gland may be slightly enlarged, but without a baseline scan performed prior to the onset of the acute attack, this change may be too subtle to detect.

Stage B: Intrinsic pancreatic changes (score 1). Stage B acute pancreatitis represents a spectrum of changes including focal or diffuse gland enlargement, mild heterogeneity of the gland parenchyma, and small intrapancreatic fluid collections caused by rupture of a small lateral side-branch duct or a small zone (< 3 cm) of parenchymal necrosis and ductal rupture.

Stage C: Intrinsic and extrinsic inflammatory changes (score 2). Stage C acute pancreatitis is manifested by intrinsic gland abnormalities as described for Stage B, but also includes mild inflammatory changes of the peripancreatic soft tissues.

Stage D: Extrinsic inflammatory changes (score 3). Patients with Stage D acute pancreatitis manifest more prominent peripancreatic inflammatory changes but not more than one ill-defined fluid collection.

Stage E: Multiple or extensive extrapancreatic fluid collections or abscess (score 4). This is the most severe CT form of acute pancreatitis and is manifested by marked intrapancreatic (fluid collections, necrosis) and peripancreatic (fluid collections, extraglandular fat necrosis) inflammatory changes, or frank pancreatic abscess formation. These patients have a high morbidity owing to systemic complications (respiratory and renal failure, cardiovascular collapse) and a high mortality. Thus, serial CT scans are important for following the progression of the disease and for detecting additional complications.

Second, the presence and extent or the absence of gland necrosis is assessed. If necrosis is present, the extent is estimated as less than one-third, one-half, or greater than one-half on the basis of the area of gland parenchyma involved as demonstrated on axial scans. A score of 0 is given if no necrosis is present, and scores of 2, 4, and 6 for less than one-third, up to one-half, and greater than one-half, respectively (Table 9).

Necrosis can be detected by CECT as a focal or diffuse area of diminished pancreatic parenchymal contrast enhancement.[79,81,84,85] In Balthazar's series, patients who had a CT Severity Index of 0–1 had no mortality or morbidity, while those with an index of 2 had a 4% morbidity, and those with an index of 7–10 had a 17% mortality and a 92% morbidity (Table 10).[76]

It should be noted that most patients with acute pancreatitis who develop necrotizing pancreatitis do so within the first 24 h and virtually all within the first 72 h following the onset of clinical symptoms. Because the CT findings of necrosis may be equivocal within the first 24–48 h, the initial CT scan obtained in patients with clinically severe acute pancreatitis should be postponed until 72 h unless the patient is critically ill and in need of emergency surgery.

The presence or absence of secondary infection of necrotic pancreatic tissue also has a significant effect on patient morbidity and mortality. In Beger's series of 114 patients with pancreatic necrosis, intestinal microorganisms were cultured from the necrotic tissue in 39.4% of cases.[49] Patients with less than 50% gland necrosis showed an increase in mortality from 12.9% to 38.9% if the necrotic tissue was infected, and patients with subtotal necrosis (> 50%), showed an increase in mortality from 14.3% to 66.7% in the presence of infection.

Computed tomography often cannot determine if necrotic tissue is infected or sterile; thus, patients with necrosis who manifest clinical signs of sepsis should undergo fine-needle aspiration (FNA) of the necrotic areas under CT or ultrasound (US) guidance to determine the presence of bacterial contamination.[1,86] From a practical standpoint, patients with necrotizing pancreatitis and obvious overwhelming sepsis need emergency surgical debridement and drainage and may not require a needle aspiration prior to surgery. Needle aspiration is most helpful in patients with necrotizing pancreatitis or large peripancreatic fluid collections and suspected sepsis with a non-improving or deteriorating clinical course despite a reasonable time of medical therapy. In these patients, a positive Gram stain or culture indicate the need for surgical or percutaneous intervention.

Recommendations for use of CECT in acute pancreatitis

The following guidelines for the use of CECT in patients with acute pancreatitis are suggested:

Initial CECT scan

1. Patients with clinically severe acute pancreatitis at the time of initial evaluation (based on Ranson criteria or APACHE II score) who do not manifest rapid clinical improvement within 72 h of conservative medical treatment.
2. Patients who demonstrate clinical improvement during initial medical therapy but then manifest an acute change in clinical status indicating a developing complication (e.g. fever, pain, inability to tolerate oral intake, hypotension, falling hematocrit etc.).

Follow-up CECT scan

1. A follow-up scan subsequent to an initial CECT which shows only Grade A–C pancreatitis (CTSI score of 0–2) is recommended only if there is a change in the patient's clinical status that suggests a developing complication;
2. A follow-up scan is recommended at 7–10 days if the initial scan shows Grade D–E pancreatitis (CTSI score of 3–10). The resolution of the CT manifestations of pancreatic and peripancreatic inflammation virtually always lags behind the improving clinical status of the patient. Thus, if the patient shows an improving clinical status, additional follow-up scans during hospitalization are recommended only if the patient's clinical status deteriorates or fails to show continued improvement. However, because some important complications can develop without becoming clinically evident early on, notably evolution of a fluid collection into a pseudocyst or development of an arterial pseudoaneurysm, a scan should be obtained at the time of hospital discharge to confirm reasonable resolution of initial grade D or E (CTSI of 3–10) pancreatitis.

The effect of CT contrast media on acute pancreatitis

Initially, concerns about CT contrast worsening the course of acute pancreatitis arose as a result of several animal studies looking at this problem. The premise for contrast worsening acute pancreatitis was based on the effects of worsening renal failure in patients with poor renal function who are given contrast. Studies in rats have examined this and also examined the effect on the capillary blood flow using intravital microscopy and demonstrated a fall in perfusion of the pancreas in pancreatitis and this correlated with an increase in mortality.[87,88] Kaiser *et al*. again looked at the effect of contrast media in a different animal model and found that CT contrast had no effect on acute pancreatitis.[89] Thus among the animal models there is no consensus that CT contrast worsens acute pancreatitis.

There are no randomized controlled trials that examine the issue of CT contrast media. One retrospective study, which examined the effects of contrast-enhanced computed tomography, did so by retrospectively examining a group of 126 patients, 52 of which underwent CT and 74 did not. Local and systemic complications were more common in the patients who underwent CT scanning. The local complication that was more frequent was pancreatic abscess occurring in 11.5% of the CT group and 0% in the other group. There were two patients in the CT group who suffered systemic complications compared to one in the non-CT group. The conclusion derived from these data was that CT scanning with contrast should be reserved for patients with severe pancreatitis.[90] This proposal concurs with the current recommended practice according to the UK guidelines on management of acute pancreatitis.[91]

Another retrospective review of the effect of CT contrast examined the outcome of pancreatitis by looking at the length of hospital stay. Two groups were identified; one group had had a CT scan and a second group who had not. The length of hospital stay was significantly longer in the CT group (10.8 days versus 6.2 days). The conclusion drawn from this study was that CT contrast might worsen pancreatitis.[92] Both these retrospective studies have limitations, because they are retrospective and subject to possible bias, such as selecting patients who are more likely to have more severe pancreatitis and complications and thus more likely to have a CT scan.

Initial management and monitoring

The majority of patients with AP have mild disease while 15–30% develop severe pancreatitis. Although only the latter suffer significant morbidity and mortality, it is wise to treat every patient aggressively until disease severity has been established.[93]

The goals of initial management are fluid replacement, electrolyte balance, caloric support, and prevention of local and systemic complications.

Depending on the local resources available and the patient's clinical condition, consideration should be given to referring a patient to a specialized center. Certainly, any patient who has severe pancreatitis or significant comorbid medical conditions should be managed in a hospital with critical care facilities. According to the British Society of Gastroenterology[91] a specialized center should be characterized by:

A hospital, which has all of the principle medical and surgical specialities;

The presence of a multidisciplinary team consisting of gastroenterologists, surgeons, intensivists, endoscopists, radiologists and pathologists;

The full-time availability of CT and US with personnel expert in invasive procedures. MRI and angiography can be helpful but are not strictly necessary;

Daily presence of an endoscopist expert in ERCP and sphincterotomy.

Resuscitation

Transudation of fluid from the intravascular space to the peritoneum is the principle cause of hypovolemia in AP. Balanced electrolyte solutions (9% saline or Ringer's lactate) should be given promptly and the rate titrated to frequent assessment of the patient's volume status determined by heart rate, blood pressure, urine output and jugular venous pressure. Following rapid administration of crystalloid solution to correct the gross volume deficit, an infusion rate should be set that accounts for basal fluid requirements (35 mL/kg per day) and ongoing third space losses. A urinary catheter should be placed to ensure outputs are accurately recorded. For patients with severe pancreatitis or those with underlying cardiopulmonary disease, a central venous catheter and occasionally a pulmonary venous catheter may, in conjunction with transfer to an intensive care unit, be required.

Laboratory evaluation of renal function, electrolytes, glucose, hematocrit and arterial pH are useful adjuncts to the clinical evaluation. Potassium chloride should be added to the intravenous fluids to achieve 100 mEq/day. Magnesium and calcium should be closely monitored and replaced if deficiencies arise. Glucose levels greater than 13.9 mmol/L (250 mg/dL) necessitate insulin administration. A blood transfusion is indicated if the patient's hematocrit is less than 25%; values ranging from 30 to 35% are considered optimal for pancreatic parenchymal perfusion.[94] Patients may have a normal blood pressure, sustaining cerebral and coronary perfusion at the expense of the splanchnic circulation. This results in pancreatic ischemia which facilitates further necrosis;[95] therefore, periodic assessments of the arterial blood gas for acidemia are recommended.[91]

Respiratory impairment is documented in 40% of cases of AP, but this tends to regress spontaneously. Oxygen saturation should be measured continuously and supplemental oxygen to maintain an arterial saturation greater than 95%. Any evidence of respiratory insufficiency requires a chest X-ray to assess for pulmonary edema or acute respiratory distress syndrome (ARDS).

Adequate and prompt fluid resuscitation is crucial in preventing the systemic complications of AP. This should be achieved within a few hours of presentation. If the volume status remains depleted despite the above measures or if fluid administration is limited by respiratory decompensation, transfer to an intensive care unit for invasive monitoring and ongoing management is needed.

If protracted vomiting occurs, an abdominal X-ray should be performed to assess for ileus and a nasogastric tube inserted to protect against aspiration. The nasogastric tube is not indicated routinely. The use of H_2 antagonists or proton pump inhibitors can ameliorate the tendency to metabolic alkalosis and prevent stress ulcers (Table 11).[93,96,97]

Analgesia

Patient comfort is essential. Patients with pain due to pancreatitis tend to have a high respiratory rate form hypoxic 'drive', which increases insensible fluid losses, decreased lung volumes from 'splinting' and reduced mobilization, which hampers lung function and increases the risk of deep venous thrombosis. Narcotic analgesics are the therapy of choice and patient administered analgesia (PCA) via an epidural catheter can be very effective. There is no definitive human study to support the widespread belief that morphine exacerbates pancreatitis by stimulating the Sphincter of Oddi to contract and difference between high dose morphine and pethidine are minimal.

Specific therapy

There does not currently exist a specific drug for the treatment of AP that is universally accepted.[91,93,96,97]

Unfortunately, most of the drugs that have shown a benefit in animal models of acute pancreatitis have had to be given prior to, at, or shortly after the onset of pancreatitis to have any ameliorating effects on the severity of the disease; a situation that rarely arises in the clinical setting with most patients presenting 12–24 h after the onset of symptoms. Correct diagnosis and staging of AP is necessary to target therapy specifically to the groups who will benefit most by them. Without the correct diagnosis and severity stratification the effects of these drugs on pancreatitis may be misleading.

Table 11 Required information and interventions in the management of acute pancreatitis

Initial presentation	Vital signs, *S*aO2, Urine output q2 h	Crystalloid i.v.
	Electrolytes, Mg, Ca, PO_4, Cr, BUN q8h	Fast
	Complete blood count	Analgesia
	ABG	Consider H_2 antagonist/PPI
	Consider chest X-ray	Consider NGT
	Consider abdominal X-ray	
Following resuscitation	Vital signs, *S*aO2, urine output q4 h	Continue above measures
	Laboratory assessment daily	Consider antibiotics
	Remove NGT once ileus resolves	Nutritional support
Transfer to an intensive care unit	Evidence of organ dysfunction	*See critical care issues in AP*

BUN, blood urea nitrogen; ABG, arterial blood gas; PPI, proton pump inhibitor; NST, nasogastric tube; AP, acute pancredtitis.

Antiproteases

An example of the above-mentioned is well supported by the observation that antiproteases, in particular gabexate mesilate,[98] when used as prophylaxis can prevent the complications in AP after ERCP.[99,100] Two meta-analyses of gabexate[101,102] suggested a significant reduction in systemic complications and need for surgery without a contemporaneous reduction in mortality.

Anti-secretive

Clinical observations have conflicting results concerning the use of somatostatin and octreotide in AP regarding morbidity and mortality[103] and these are not recommended.

Platelet activating factor antagonist

Promising pilot studies suggest a benefit with the platelet activating factor antagonist, Lexipafant (British Biotech Pharmaceuticals, Oxford, UK). A recent double-blind study demonstrated a significant difference in mortality among treated patients and matched controls.[104] Unfortunately, a larger study did not confirm any advantage in terms of mortality rate,[105] thus its routine use is not recommended.

Antibiotic prophylaxis

Infectious complications are still regarded as the primary cause of mortality in severe pancreatitis.[106] Thus, it is essential to identify the presence of pancreatic necrosis and take measures to prevent infection.

The antibacterial drug chosen for a patient with pancreatic necrosis should have a spectrum of action consistent with the primary pathogens responsible for pancreatic infection and should penetrate into the pancreatic parenchyma. Recent evidence suggests that antibiotics active against Gram-negative bacteria, the prevailing cause of pancreatic infection[107] are secreted into the pancreatic juice[108,109] and necrotic tissue[110] at therapeutic concentrations. Six randomized trials,[111–116] have demonstrated a reduction in infected necrosis, surgery, morbidity and, in one study,[115] mortality in patients with severe pancreatitis (Table 12). Furthermore, a subsequent meta-analysis containing five of these studies confirmed a reduction in mortality in the group treated with antibiotics.[117]

The current recommendation is the use of a systemic antibiotic such as imipenem-cilastatin 500 mg three times a day for 2 weeks[16,111,114] in patients with documented pancreatic necrosis.

While the use of broad-spectrum prophylactic antibiotics has significantly reduced the incidence of infected necrosis, there is a changing spectrum of microorganisms responsible for infected necrosis. For instance, the Verona group published an early experience of 15 patients with infected necrosis primarily due to Gram-negative bacteria of gastrointestinal origin.[114] However, in a recent report of 13 patients with infected necrosis, the causative microorganisms were methicillin-resistant *Staphylococcus aureus* and *Candida glabrata*.[111] This observation is widely confirmed by others[2,118–121] and represents a serious problem, as fungal infection, even when appropriately treated, has a high mortality rate.[124] Although the early administration of low-dose fluconazole, has been evaluated,[118,123] selection of resistant fungal species could result.[124] The challenge is to identify infected necrosis and initiate early antibiotic prophylaxis. An acceptable strategy would be to perform a CT scan with intravenous contrast at days 4–7 and begin imipenem if necrosis is present. The use of early antibiotic treatment with imipenem has been shown to decrease the need for surgical intervention.[125] If there is clinical evidence of infection, pancreatic necrosis should be sampled by CT-guided fine needle aspiration (FNA).[126] If infection is confirmed, the tissue should be treated by surgical debridement, either via open access or percutaneously.

Table 12 Pancreatic infection incidence and mortality rate in controlled trials with antibiotics

Author	Antibiotic	No. patients	Pancreatic infection (%)		Mortality (%)	
			Control	Case	Control	Case
Pederzoli *et al.*[114]	Imipenem	74	30	12★	12	7
Luiten *et al.*[113]	SDD	102	38	18†	35	22
Sainio *et al.*[115]	Cefuroxime	60	40	30	23	3★★
Delcenserie *et al.*[112]	Ceftazidime, amikacine & metronidazole	23	58	0†	25	9
Schwarz *et al.*[116]	Ofloxacin & metronidazole	26	53	61	15	0
Bassi *et al.*[111]	Pefloxacin *vs* imipenem	60	Pefloxacin 34	Imipenem 10†	Pefloxacin 24	Imipenem 10

SDD, selective digestive decontamination (see text); ★$P < 0.01$; ★★$P = 0.028$; †$P = 0.03$.

Nutritional support

Acute pancreatitis is a hypercatabolic state resulting in rapid loss of body weight, fat and protein.[127–129] Nutritional support is an integral part of patient care and is started early in the course of disease. Patients with mild to moderate disease (80% of patients) do not require jejunal or parenteral nutrition, as they will begin oral feeding within 4 days of presentation.

In patients with severe pancreatitis either total parenteral nutrition or total enteral nutrition is employed. The leading groups in the UK and continental Europe now employ early enteral nutrition in preference to intravenous feeding in patients with severe AP. A naso-enteral tube is inserted under endoscopic or fluoroscopic guidance on day 3 or 4 and a semi-elemental diet begun. This should have a concentration of 4.184 J/mL. If tolerated, the feeding is advanced to a polymeric formula. Most groups have used nasojejunal feeding, which has difficulties in maintenance of the tube position and patency.

It has traditionally been considered that any form of enteric feeding during the acute phase of illness was contraindicated because an exacerbation of AP would result. Intensive care studies in patients with trauma and sepsis showed that enteric feeding was associated with a reduction in the acute phase response and the severity of septic complications compared to total parenteral nutrition (TPN).[130] A French study in 1997 pointed to 20% of patients experiencing pain relapse on refeeding[131] such that few have tried naso-enteric feeding until the last few years.

A consecutive study of 21 patients all with objective evidence of severe AP in Brussels showed the feasibility of the use of a double lumen nasogastrojejunal tube in 20 patients.[132] In the USA, a study of patients with mild or moderate AP found that randomization to nasojejunal feeding was better than TPN in that there was no significant difference in clinical outcome but a considerable reduction in cost and morbidity associated with naso-enteral feeding.[133]

A randomized clinical study of 38 patients with severe AP by Kalfarentzos *et al*. comparing nasojejunal feeding with TPN again found little difference except in cost and the complications of TPN. In this study the mean APACHE II score was over 11.5 (Glasgow score over 4) and CRP values were over 280 mg/L. The total number of days in intensive care and overall hospital stay showed no statistical difference. Mortality was similar in both groups but the cost of therapy was US$45 per day in the nasojejunal feeding group and more than three times this in the TPN group.[134]

A much smaller randomized study of 34 patients from the UK found only 13 with objective criteria of severe AP. Although these patients were evenly divided between the two treatment groups there was a tendency to poor results in the TPN group who had a higher morbidity and mortality. There was a lower SIRS scoring in the group fed enterally and also a lower IgM anticore endotoxin antibody level in those fed enterally.[135]

A recent publication on a group of 26 patients with prognostically severe AP were all fed by fine-bore nasogastric tube soon after admission. This was shown to be both practical and safe in 22 of the 26 patients. Feeding began within 48 h of hospital admission and starting with 30 mL/h it was possible to increase the feed to 100 mL/h in most of these patients within a further 36–48 h of treatment

Subsequently, a randomized study of nasogastric versus nasojejunal feeding in severe AP has shown little difference in terms of CRP response, pain, analgesic input or clinical outcome from these two approaches to early naso-enteric feeding.[136] All of these studies are still rather small but the indication is that clinical practice, particularly in continental Europe and the UK is swinging towards the early use of naso-enteric feeding with a lowering of the risk to the patient associated with TPN.

If enteral nutrition is not tolerated, parenteral nutrition is required. The preferred solution contains carbohydrate, protein and lipid. The exception to this is hypertriglyceridemia, in which case lipid should be excluded. A patient's individual caloric requirement is calculated using the Harris-Benedict equation with appropriate modifications for stress factors[137] or using indirect calorimetry. In general, patients with severe acute pancreatitis require 8000–10 000 kilojoules/day: 50–60% from glucose, 15–20% from protein and 20–30% from lipid.

Management of gallstone pancreatitis

Gallstones are the leading cause of acute pancreatitis in many Western and Asian countries.[138–140] In Western countries, acute biliary pancreatitis (ABP) is responsible for 34–54% of the 4.8–24.2 cases per 100 000 per year of acute pancreatitis. Case-fatality in severe pancreatitis remains unacceptably high. Despite modern intensive care management, approximately 10% of patients with acute pancreatitis die during hospitalization.[139]

While the exact pathogenesis of ABP is still being pursued, its urgent management has increasingly included early endoscopic intervention.[138,140] Endoscopic intervention allows effective removal of the offending stone(s) and re-establishment of biliary drainage. The success rates of endoscopic management, in expert centers, exceed 90%;[138,140–142] Observational data[143,144] and, more importantly, randomized controlled trials (RCT) have spearheaded the widespread use of endoscopic therapy for the management of ABP. Four randomized controlled trials involving more than 800 patients in Western and Asian countries have been completed.[138,140–142]

Endoscopic treatment of acute biliary pancreatitis

In addition to supportive care, common to all types of acute pancreatitis, early endoscopic therapy has become increasingly integrated into the treatment for severe ABP over the last decade. The support for use of ERCP and ES came from observational reports and randomized trials.[138,140–144] The landmark RCT of ERCP and

ES began in 1983[140] after sporadic case reports from various centers around the world reported rapid improvement of patients with ABP after establishment of biliary drainage and normalization of laboratory values. At the completion of this trial in 1987, the concerns of exacerbation of pancreatitis, cholangitis, hemorrhage, and perforation induced by ERCP and ES were not realized.[140] Instead, the benefits of early ERCP and ES performed on patients with severe ABP were substantiated. Three studies have since been completed following the publication of the first RCT by the Leicester group in 1988.[138,141,142]

Randomized clinical trial from the UK

The Leicester group in England randomized 121 patients with suspected ABP to receive either conventional conservative treatment or to undergo urgent ERCP within 72 h after admission.[140] Patients who were found to have choledocholithiasis underwent ES and stone extraction. The severity of pancreatitis was classified according to the modification of the Glasgow criteria.[145] Fifty-nine patients, 25 of whom had severe pancreatitis, were randomized to ERCP. Sixty-two patients, 28 of whom had severe pancreatitis, underwent conventional treatment. ERCP was successful in 94% of mild and 80% of severe attacks while choledocholithiasis was found in 25% and 63% of patients predicted to have mild and severe attacks, respectively. All bile duct stones were removed endoscopically without complication. This study provided four important findings: (i) ERCP could be safely performed in an expert center; (ii) ERCP reduces the morbidity (61% in the conventional group compared to 24% in the ERCP group) and mortality (18% in the conventional group compared to 4% in the ERCP group) of patients who were classified to have severe pancreatitis; and (iii) ERCP reduces the hospital stay for those with severe pancreatitis.

Randomized clinical trial from Hong Kong

A second RCT was performed by the Department of Surgery, University of Hong Kong.[138] The high prevalence of gallstones as the cause of pancreatitis in Hong Kong allowed these investigators to enrol all patients with acute pancreatitis. They randomized 195 patients with acute pancreatitis to early ERCP (within 24 h of admission) and conventional treatment. A severe attack was categorized when the patient had a serum urea concentration above 45 mg/dL and plasma glucose concentration exceeding 198 mg/dL on admission. While the results and conclusions of the Hong Kong study might not be generalized worldwide because of differences in the incidence of gallstones as the cause of pancreatitis, this study provided important information for the management of ABP.

Subgroup analysis of patients who had gallstones and bile duct stones from the Hong Kong study confirmed the results of the UK study. One hundred and 27 patients (65%) were proven to have biliary stones. Ninety-seven patients were randomized to ERCP within 24 h and 64 patients were diagnosed to have gallstones. Endoscopic sphincteroplasty was performed on 37 patients who had choledocholithiasis. In the 63 patients with gallstones who were treated with conventional treatment, 22 deteriorated and underwent ERCP—10 had bile duct stones and gallbladder stones. Patients who were predicted to have severe pancreatitis fared significantly better. The morbidity was decreased from 54% to 13% and the mortality was lowered from 18% to 3%. The RCT from Hong Kong, like that from the UK, did not find any difference in the outcomes of patients with mild acute pancreatitis who were treated with ERCP versus conventional treatment.

As both the UK and Hong Kong studies were single center studies, concerns have been raised about the reproducibility of their results in day-to-day practice. Unfortunately, other studies with similar designs have not been forthcoming. There are many logistical and perhaps also ethical barriers that may have prevented similar studies to be performed. Others have questioned the severity of 'severe' patients as predicted by the modified Glasgow, and serum urea and glucose levels used in the UK and Hong Kong studies, respectively. While these predictors have some limitations, they are practical to use and have adequate sensitivity and specificity. The validity of these predictors is now accepted and they are widely applied to stratify patients.

Randomized clinical trial from Germany

The third study was a prospective multicenter study in which 238 patients with ABP who had no evidence of obstructive jaundice were randomized to early ERCP (within 72 h) or conventional treatment.[141] Of the 126 patients assigned to early ERCP, this was successful in 121 patients (96%), and 58 had bile duct stones. Twenty of the 112 patients in the conservative-treatment group subsequently underwent ERCP and 13 of these had bile duct stones removed. There were no significant differences in the mortality and morbidity rates between the two groups. However, patients who received early ERCP had a higher incidence of respiratory failure and more severe complications. Stratification of patients according to the severity of disease did not affect their findings.

The patients included in this study were confined to those patients with ABP without evidence of obstructive jaundice. Its results might thus be interpreted that a subgroup of patients (those with ABP who had no evidence of biliary obstruction) can be treated conservatively without urgent ERCP. However, many concerns have been raised regarding the design and results of this study.[146] A confirmatory study is required before its findings are accepted into daily practice.

The first concern applies to the small number of patients enrolled by each center. In comparison to the first two studies, which were single center, the RCT from Germany included 22 centers but enrolled only 238 patients (as compared to 121 and 195 patients in

the UK and Hong Kong studies, respectively) over a longer study period. On average, 10.8 patients (range 6–29) were enrolled at each center over a 54-month period, or 2.4 patients/center per year. Three centers had 20 or more patients, thus, on average, the remaining 19 centers included fewer than 2 patients/year. It is known that ERCP and ES are technically demanding procedures and expertise varies with, among other factors, the level of experience.[146] The low enrolment number of study patients per participating center per year reported in the German study might potentially confound their results as it could reflect inadequate level of ERCP expertise or available ABP patients in some participating centers.

The second concern addresses the finding of a five-fold increased risk of respiratory failure (as defined by the inability to maintain partial pressure of oxygen above 60 mmHg with an oxygen mask) in patients who were assigned to early ERCP ($P=0.03$). While hypoxemia is common in patients with severe pancreatitis, early ERCP did not increase the incidence of respiratory failure in the UK and Hong Kong studies. The German Study Group on acute biliary pancreatitis also found a trend of higher mortality occurring among patients who received early ERCP. In comparison, the UK, Hong Kong and the fourth study from Poland reported lower rates of mortality in patients who had early ERCP intervention. Whether the significance of increased incidence of respiratory failure or the trend of higher mortality in the ERCP group in the German trial is due to overuse of statistical significance (the cut-off P value should be corrected with increasing number of comparisons instead of using cut-off $P=0.05$ (Bonferroni correction)) or due to other reasons is unclear.

Randomized clinical trial from Poland

The fourth study was completed in Poland and was recently reported in abstract form.[142] Here, the design involved the inclusion of 280 patients with ABP all of whom underwent duodenoscopy within 24 h of admission. Seventy-five patients were found to have impacted stone in the papilla and received immediate ES. The remaining patients were randomized to immediate ES or conventional treatment. Like the UK and Hong Kong studies, but unlike the German study, they found significantly fewer complications in the group who had ERCP and ES (17% *vs* 36%, $P<0.001$, lower mortality rates among patients who had ES (2% *vs* 13%, $P<0.001$), and lower morbidity and mortality the earlier the ERCP was performed. They also found that the benefits of ERCP and ES extended to patients predicted to have mild pancreatitis. Extensive analysis of this study, however, will require its full report.

Summary results of the randomized clinical trials

The designs of the four randomized controlled trials differ. There are also ethnic, environmental, and perhaps level of endoscopic expertise differences reported in these studies. It is not surprising that an attempt to combine the results of these trials into a single recommendation is difficult.

To date, there are two well-performed published studies (UK and Hong Kong) that support early endoscopic intervention in patients with ABP. Their results suggest that patients with severe disease are likely to have decreased morbidity and mortality. The applicability of their results has been questioned by the RCT from Germany that suggested that patients without obstructive jaundice would not benefit from early endoscopy. However, the German study actually may complement the earlier studies because it specifically excluded patients that were included in the UK and Hong Kong trials. Preliminary findings from Poland suggest that all patients, irrespective of the severity of their disease, would benefit from early endoscopic intervention. A recent meta-analysis supports these conclusions.[147] (Fig. 1)

Preferred management of acute biliary pancreatitis

The available literature has provided us with guidance on an approach, which theoretically will maximize favorable patient outcome. Urgent ERCP should be performed in patients with acute pancreatitis of suspected or proven gallstone etiology when criteria for severity are met and/or there is coexistent cholangitis, jaundice, dilated CBD, or when there is clinical deterioration in patients with initial mild prognostic signs. As ES almost certainly protects against recurrence of gall-

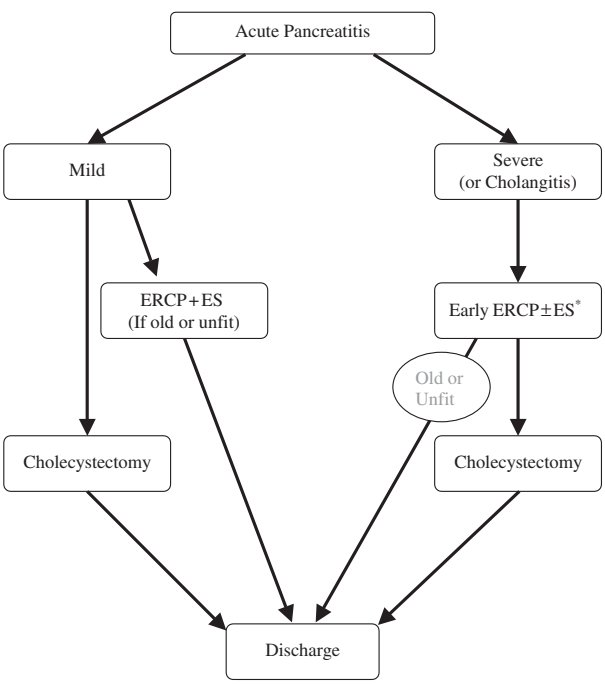

Figure 1 Management of acute biliary pancreatitis.

stone pancreatitis, it is recommended in a patient with severe gallstone pancreatitis with significant local and/or systemic complications, a dilated bile duct without demonstrable stones, and a gallbladder containing stones, if cholecystectomy is neither possible nor contemplated.

Timing of cholecystectomy

The indications for and appropriate time interval between acute gallstone pancreatitis and cholecystectomy are determined by the presence of an ES and the severity of the pancreatitis. An adequate ES should allow gallstones to pass into the duodenum[148,149] and thus provide protection against further pancreatitis. However, there are several series demonstrating an ongoing risk for cholecystitis following ES in patients with an intact gallbladder with a probability of 1–11%.[150–152] The presence of cholelithiasis at initial ERCP is associated with the highest risk of acute cholecystitis. Most experts agree that an otherwise healthy patient should proceed to definitive surgical management but, for those at high surgical risk, ES alone may be sufficient. In the absence of an ES the risk of a second attack of pancreatitis is sufficiently high, at least 50% in the short term,[153,154] such that patients should be offered laparoscopic or open cholecystectomy with intraoperative cholangiography during the same hospital admission. It is advocated that no patient should be discharged after an episode of acute gallstone pancreatitis without undergoing definitive therapy for gallstones. Bile duct stones demonstrated intraoperatively can be removed surgically or by postoperative ERCP. Although it appears to be safe to operate on patients with mild pancreatitis, patients with severe pancreatitis should not be operated on in the first 48 h after admission as there is a higher complication rate and operative mortality.[155–158]

Critical care issues in severe acute pancreatitis

Severe acute pancreatitis often evolves into SIRS, which can lead to MODS. Systemic inflammatory response syndrome and MODS are the common final pathway of inflammation resulting from any causes. These patients need to be closely monitored and may require management in a critical care unit (Table 13).[159]

Table 13 Definition of SIRS and MODS

Systemic inflammatory response syndrome (SIRS)	≥ 2 of the following: Temperature > 38°C or < 36°C Heart rate > 90 b.p.m. Respiratory rate > 20 $PaCO_2$ < 32 White blood cells > 12 000 or < 4000 mm^3 Immature neutrophils > 10%
Multiple organ dysfunction syndrome (MODS)	SIRS ≥ One vital organ dysfunction Acute respiratory distress syndrome (ARDS) Acute renal insufficiency Hypotension Disseminated intravascular coagulation (DIC) Acute adrenal insufficiency Acute hepatitis Metabolic encephalopathy Ileus

Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is a manifestation of systemic inflammation or primary injury to the lung. It is thought alveoli become filled with an inflammatory exudate impeding gas exchange with resulting hypoxemia refractory to supplemental oxygen therapy. Chest X-ray classically demonstrates bilateral, diffuse pulmonary infiltrates. Acute respiratory distress syndrome and cardiogenic pulmonary edema are difficult to distinguish clinically. In the latter, the pulmonary capillary wedge pressure is > 18 mmHg.

Management consists of intubation and mechanical ventilation. Due to the patchy lung involvement, patients with ARDS are at higher risk of both pressure and volume-related lung injury during mechanical ventilation. Tidal volumes of < 10 mL/kg and peak inspiratory pressures of < 35 cmH2O are advised. Positive end-expiratory pressure is then used to prevent alveolar collapse and decrease F_iO_2.[160]

Acute renal failure

In the setting of acute pancreatitis, acute renal failure (ARF) may be due to decreased renal perfusion pressure, as seen in hypotension and hypovolemia, or may be the result of acute tubular necrosis (ATN). The exact pathogenesis of ATN is not well understood but likely involves an ischemic insult and inflammatory injury to the renal tubular cells. The clinical hallmark is acute oliguria. The diagnosis of ARF is made if one of the following is present:[161] (i) increase in serum creatinine > 0.5 mg/dL (44 μmol/L) or 50% above baseline; (ii) reduction in the calculated creatinine clearance > 50%; or (iii) a need for dialysis.

To distinguish a prerenal (hypotension or hypovolemia) cause of oliguria from a renal cause (ATN), the fractional excretion of sodium (FENa) may be useful. In general, if the FENa is < 1% then prerenal disorder is present and FENa > 2% implies intrinsic damage to the kidneys.

Treatment is supportive. Hemodynamic parameters must be optimized and dialysis instituted if necessary.

Hypotension

Patients with acute pancreatitis and SIRS may develop hypotension (mean arterial pressure < 60 mmHg) associated with a hyperdynamic circulation. Decreased systemic vascular resistance leads to vasodilation and increased cardiac output. Clinically, patients will have an increased heart rate, increased peripheral pulse amplitude and warm skin. This is in contrast to patients with a decreased blood pressure due to inadequate volume resuscitation who will have a hypodynamic circulation.

Appropriate management consists of close hemodynamic monitoring and support with intravascular volume administration and inotropic medications if indicated.

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is a rare complication of acute pancreatitis. The coagulation system is activated by a tissue factor, resulting in intravascular coagulation. Consumption of platelets and coagulation factors leads to thrombocytopenia, prolonged clotting times and a risk of hemorrhage. Fragmented red cells, schistocytes, are due to physical trauma from the cross-linking fibrin. Fibrinogen levels are classically low but as fibrinogen is an acute phase reactant the level may be within the normal range. Management is difficult and should involve consultation with a hematologist. Likewise, heparin therapy should be considered with thrombosis.[162]

Metabolic encephalopathy

The encephalopathy observed in SIRS is due to cerebral ischemia. Patients have a decreased level of consciousness. Electroencephalogram (EEG) changes may be present. Management entails hemodynamic support and avoiding medications that may exacerbate alterations in sensorium. Prognosis depends on severity.

Pancreatic encephalopathy is used to describe delirium, which may be associated with dysarthria and limb rigidity. The exact pathogenesis is not well understood. It may be the result of circulatory insufficiency as described above, a separate entity or misdiagnosed delirium tremens.

Intermediate management

After the first week of illness the main problems concern continuing organ failure and sepsis in the necrotic peripancreatic or pancreatic tissues. Patients who have not recovered from major organ compromise or failure by the end of the first week of management represent the highest mortality and morbidity and the focus upon infection without consideration of organ failure is unwise. Most of the literature focuses on only the presence of sterile or infected necrosis and the consensus view is that sterile necrosis does not require surgical intervention in most patients. However, where new organ failure is developing the case may be advanced that such patients warrant consideration for surgical intervention on the possible premise that FNA has provided a false negative, but also that some patients with sterile necrosis do benefit from surgery where a new situation is developing clinically such as movement from respiratory compromise to failure or similarly, and possibly at the same time, cardiac decompensation with parallel events in the kidneys.

Late complications

Late complications of acute pancreatitis include fistulae from the pancreatic duct and gastrointestinal tract, pseudocyst formation, pancreatic abscess, and vascular complications (mesenteric venous thrombosis and arterial pseudoaneurysms). A variety of radiological imaging procedures can be used to detect these complications, including CT, MRI, US, angiography, contrast studies of the gastrointestinal tract, and ERCP.[77]

In general, contrast-enhanced CT is the single best imaging modality for evaluation of patients with acute pancreatitis. It can differentiate between edematous and necrotizing acute pancreatitis and detect most of the complications of both types. Contrast-enhanced MRI can be used in place of CT if there is a contraindication for administration of intravenous contrast medium. The other modalities, such as ERCP and angiography, play a more specific role in evaluation of the pancreatic and biliary ducts and the vascular system. Ultrasonography is most useful for routine follow up of a known fluid collection or pseudocyst.

Fistulae

Pancreatic duct disruption may occur in an attack of acute necrotizing pancreatitis. In some cases, the ductal disruption heals spontaneously. More often, however, the disruption persists and results in a focal collection of pancreatic juice, which will evolve into a pseudocyst, or leak directly into the peritoneal cavity, resulting in pancreatic ascites. Endoscopic retrograde cholangiopancreatography is the best technique for demonstrating pancreatic duct disruption and plastic stents facilitate healing.[163,164]

Gastrointestinal fistulae may be caused by direct erosion of the inflammatory process into a contiguous segment of the gastrointestinal tract or by erosion or direct extension of an abscess or pseudocyst. Virtually any segment can be involved, but most commonly this occurs into the duodenum or transverse colon.[165–170] Gastrointestinal fistulae often are demonstrated with CT following administration of an oral contrast agent. The orally administered contrast leaks into the peripancreatic space or into a pancreatic fluid collection, abscess, or pseudocyst. In some cases, a contrast examination of the gastrointestinal tract may be useful to depict the precise location of the fistula.

Pseudocyst

Acute pancreatic fluid collections occur in about 40% of patients with acute pancreatitis. In these patients, about 50% of the collections will resolve spontaneously and about 50% will evolve into a pancreatic pseudocyst.[171] Pseudocysts can be identified by any of the cross-sectional imaging modalities. However, contrast-enhanced CT is believed to be the best technique as it identifies the pseudocyst, accurately depicts its relationship to surrounding structures, and detects any secondary complications, such as involvement of the gastrointestinal tract, obstruction of the pancreatic or biliary duct, compression or occlusion of the mesenteric veins, or formation of an internal arterial pseudoaneurysm.[172] Contrast-enhanced MRI can be used if there is a contraindication for use of intravenous contrast for CT.

Endoscopic retrograde cholangiopancreatography can be used if it is necessary to determine if there is a communication between the cyst and the pancreatic duct. This may be required prior to some forms of interventional therapy, particularly endoscopic pancreatic duct stent placement.[173,174] If clinically necessary, an uncomplicated pseudocyst may be followed by US to assess change in size or to determine if the cyst is resolving.

Pancreatic abscess

Pancreatic abscess is defined as a circumscribed intra-abdominal collection of pus in close proximity to the pancreas and containing little or no pancreatic necrosis.[175] Abscesses may or may not contain gas. They can be detected by each of the cross-sectional imaging modalities. However, CT is the most accurate at detection, depicting the anatomical location and relationship to surrounding structures, and identifying associated complications, particularly fistulae to the gastrointestinal tract and vascular complications (venous compression or thrombosis, arterial pseudoaneurysm).[176] In addition, as the presence of infection within a fluid collection is only determined by culture of the contents, a CT or US scan, used at the time of initial detection of the collection, allows the safe collection of a percutaneous aspirate for culture.[86,177]

Vascular complications

Acute pancreatitis can cause mesenteric venous compression or occlusion (splenic or superior mesenteric vein) with subsequent prehepatic portal hypertension, direct erosion of a pancreatic or peripancreatic artery or vein with hemorrhage, or formation of an arterial pseudoaneurysm. Contrast-enhanced CT or MRI are suitable for the detection of vascular complications.[77,178] In some cases, if the targeted vessel can be identified with US, Doppler interrogation is useful to detect vascular compression or occlusion. If more precise information is required, selective visceral angiography may be required.[179,180] Angiography has the added advantage of being able to control active hemorrhage or occlude pseudoaneurysms.[181]

The role of surgery in acute pancreatitis

It is nowadays rare for the diagnosis to be made at surgery as the clinical presentation of acute onset upper abdominal pain and vomiting together with raised levels of amylase and/or lipase normally point to the diagnosis of acute pancreatitis. Substantiation can be obtained from either MR or CT imaging and, where there is genuine diagnostic doubt, peritoneal aspiration may help differentiate acute pancreatitis from a perforated DU or ischemic bowel. In those two conditions the fluid is usually smelly and contains bacteria whereas it is normally sterile in the early phase or acute pancreatitis.

Should the diagnosis be made unexpectedly at immediate laparotomy, then cholecystectomy with operative cholangiography is relevant in the majority of patients as this is the most common etiology and the pancreas should not be unnecessarily handled at this stage of the disease, but clearance of any stones in the CBD is wise.

Surgery in necrotizing acute pancreatitis

There is increasing non-randomized evidence from sequential audit that sterile pancreatic necrosis can be successfully managed by continued conservative therapy (Fig. 2). In a large retrospective analysis of a prospective audit, it is reported that in the Swiss experience in Bern few, if any, patients die in the first 2 weeks of illness provided antibiotic therapy is routinely available.[2] While the general guideline of conservative management for sterile necrosis versus active intervention for infective necrosis is agreed, there is certainly a considerable need for further studies.

Some have argued that a lack of stabilization or improvement with full supportive intensive care therapy over 72 h should constitute an indication for surgical intervention to establish intra-abdominal peritoneal lavage, but no randomized study has validated this approach. When a patient has clinical evidence of sepsis (usually >7 days of onset) unexplained by normal

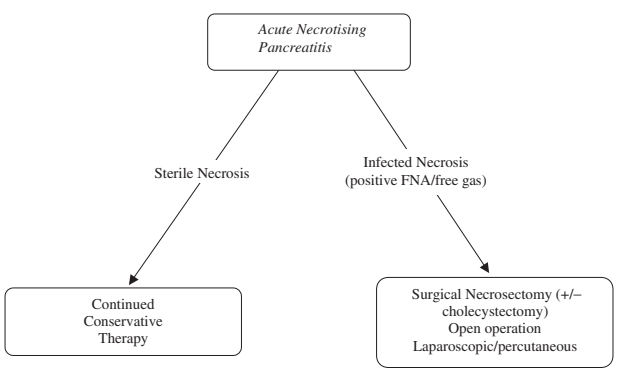

Figure 2 Management of necrosis.

microbiology studies a CT scan should be performed and FNA with immediate Gram stain and subsequent culture of the fluid. The odour of the fluid itself may indicate sepsis. In such situations active intervention to remove the pus and adjacent peripancreatic or pancreatic necrosis is mandatory. In very ill patients a percutaneous drain may be placed at the time of FNA using CT guidance. Such drainage of pus may allow further stabilization of the patient before removal of the infected necrotic tissue.

Types of surgical approach

Traditionally, an anterior open surgical approach either through a transverse upper abdominal or a vertical incision has been routinely advocated with exploration of the area of necrosis and infection, using digital dissection or gentle instrumentation, to remove the dead tissue. Preoperative imaging should guide the surgeon to the area of dead tissue but suboptimal or absent imaging necessitates checks down the paracolic gutters as well as the pancreas and peripancreatic area. In a proportion of patients the transverse colon may be compromised and when genuine doubt exists, it is wiser to perform an extended right hemicolectomy with the formation of an ileostomy and mucous colonic fistula (or closed-over colon) than to leave behind compromised transverse colon. Postoperatively, lavage through strategically placed drains should continue at a rate of 1–2 L/day and this may be required for 3 to 4 weeks with a 30% chance of a repeat operation being necessary because of recurrent sepsis.

Where venous bleeding and oozing of blood is particularly troublesome packing of the upper abdomen with large cotton packs enclosed in paraffin gauze or a similar non-adherent material may be necessary. The main wound may be left open (laparostomy) or closed but reoperation to change the packs will be necessary. At this second operation if there is no bleeding, it may be possible to establish a peritoneal lavage set-up through multiple drains. The alternative of regular packing every 48 h until granulation tissue heals over the area is both hard work and very time-consuming.

Alternatives to open surgery that are being actively investigated include both anterior laparoscopic and retroperitoneal percutaneous approaches. The relative merit of these different types of surgery has not been subject to critical evaluation, but the lesser trauma of the operation may be of advantage in older patients or those in multi-organ failure.

As one of the major purposes of surgical therapy in severe AP relates to minimizing the risk of a further episode of pancreatitis it is logical and wise to remove the gallbladder and check for any residual stones in the CBD at the same operative procedure.

Acute fluid collections, pseudocysts and abscesses

In Fig. 3 a summary of the pattern of evolution of acute fluid collections in and around the inflamed pancreas is outlined. Sequential study has resulted in the knowledge that approximately 50% of acute fluid collections resolve spontaneously and quite rapidly within the first 4 weeks of illness. Failure of resolution can lead to the formation of a circumscribed or multilocular sterile pseudocyst. This usually takes around 4 weeks to develop from the onset of AP and approximately 50% of these will resolve spontaneously. Those that persist may cause local pressure effects with obstruction of the duodenum or CBD and compression effects on the stomach from the most common location adjacent to the body and tail of pancreas. When infection develops this is correctly described as a pancreatic or peripancreatic abscess. The therapy of both pseudocyst and abscess is similar with either internal or external drainage methods being used.

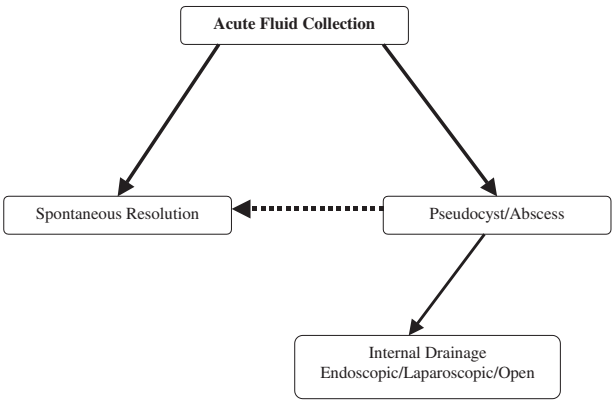

Figure 3 Management of fluid collections.

Persistent pancreatic pseudocyst

Where severe compression effects are occurring decompression may be necessary in a fairly urgent manner with optimum results being obtained by internal drainage which can be afforded by endoscopic stent placement in a long disrupted pancreatic duct or directly placing the stent into the pseudocyst through the wall of the stomach or duodenum. Alternative therapy includes either open or laparoscopic surgery with the formation of an anastomosis between the pseudocyst and part of the gastrointestinal system (stomach, duodenum or Roux loop of jejunum). No randomized study has been performed comparing endoscopic with surgical approaches and availability or local expertise often determines which approach is first used. Studies do exist indicating that internal drainage is much safer than external drainage with lower morbidity, mortality and recurrence of pseudocysts.

Pancreatic abscess

Results of therapy for pancreatic abscess are much better than the treatment of infected pancreatic necrosis. The abscess tends to be circumscribed and may be

treated by methods identical to pancreatic pseudocyst but external drainage is favored more frequently for this problem. Infected necrosis frequently is accompanied by organ failure whereas abscess is a later complication not usually associated with the same phase of major illness.

Summary and levels of evidence

Acute pancreatitis, as defined by the Atlanta classification, is an acute inflammatory condition of the exocrine pancreas. The current incidence ranges from 10 to 80/100 000 population per year and the overall mortality ranges from 2 to 10%. The incidence in males is usually 10–30% higher than in females.

The commonest cause is gallstones with alcohol being the next most common cause.

Patients with acute pancreatitis present with upper abdominal pain and/or different degrees of organ failure.

The diagnosis is suspected by a typical clinical presentation and supported by raised serum amylase. Atypical presentations may require confirmation by CT imaging.

Immediate management comprises analgesics, intravenous fluids and monitoring.

No benefit has been demonstrated with the use of aprotinin, glucagon, somatostatin, octreotide, purified plasma derivatives, gabexate mesilate and lexipafant for the treatment of acute pancreatitis (Level II).

Acute pancreatitis has a continuum of severity best defined by failure of one or more organ systems and/or the Acute Physiology and Chronic Health Evaluation, Mark II (APACHE II) score of 8 or more.

Gallstone etiology is usually identified by early routine abdominal ultrasonography.

The majority of patients have mild pancreatitis and recover without additional treatment.

In 20%, the disease is severe and is associated with a mortality of about 20%.

Patients with severe pancreatitis require management in a high dependency or intensive care setting; this may require transfer to a specialized unit.

Clinical severity is paralleled by the degree of pancreatic and peripancreatic tissue necrosis as defined by dynamic CT.

Antibiotic prophylaxis is advised in patients with greater than 30% necrosis and imipenem is recommended currently (Level I).

Enteral nutrition probably retains the integrity of the intestinal mucosal barrier and hence early mesenteric feeding is recommended (Level II). Parenteral nutrition is rarely indicated.

In patients with severe gallstone pancreatitis, early endoscopic retrograde cholangiography is indicated and, where appropriate, a sphincterotomy and clearance of the bile duct (Level II).

Where infection of pancreatic necrosis is proved by the presence of positive FNA or free gas in the area of necrosis, surgical intervention is indicated (Level III).

In sterile necrosis, continued conservative management is justified (Level III).

Patients with gallstone pancreatitis should either undergo cholecystectomy or endoscopic sphincterotomy and bile duct clearance prior to discharge (Level III).

Acute fluid collections are a feature of severe acute pancreatitis and often resolve spontaneously (Level III).

Pancreatic and peripancreatic abscesses, symptomatic pseudocysts and other ductal disruptions require interventional treatment (Level III).

Splenic arterial/venous and portal vein thrombosis rarely require intervention (Level III).

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