International Journal of Pancreatology, vol. 25, no. 3, 195–210, June 1999

0169-4197/99/25:195–210/$14.00

Consensus Document

Diagnosis, Objective Assessment of Severity, and Management of Acute Pancreatitis

Santorini Consensus Conference

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Summary

Background: The diagnosis, early assessment, and management of severe acute pancreatitis remain difficult clinical problems. This article presents the consensus obtained at a meeting convened to consider the evidence in these areas. The aim of the article is to provide outcome statements to guide clinical practice, with an assessment of the supporting evidence for each statement.

Method: Working groups considered the published evidence in the areas of diagnosis, assessment of severity, nonoperative treatment, and surgical treatment of severe acute pancreatitis. Outcome statements were defined to summarize the conclusions on each point considered. The findings were discussed and agreed on by all participants. A careful assessment was made of the strength of the available evidence (proven, probable, possible, unproven, or inappropriate).

Findings and Conclusions: There is reliable evidence to support much current practice. Clear guidance can be given in most areas examined, and several areas were identified where further investigation would be helpful. Diagnosis using plasma concentrations of pancreatic enzymes is reliable. Rapid advances are taking place in the assessment of severity. Several new therapeutic strategies show real promise for the reduction of morbidity and mortality rates. Surgical debridement is required for infected pancreatic necrosis, but is less often necessary for sterile necrosis.

Introduction

Acute pancreatitis is a potentially lethal disease with wide variation in clinical features and severity, ranging from mild and self-limited to a rapidly progressive illness leading to multiple organ failure and death. Mortality rate ranges from nil in mild disease to 10% with sterile and 25% with infected pancreatic necrosis.

Acute pancreatitis can be difficult to diagnose accurately. Autopsy studies show a high incidence of acute pancreatitis not diagnosed in life *(1,2)*. Therefore, improvements in the diagnosis of acute pancreatitis are essential.

There is a lack of precise criteria for accurately predicting severity and monitoring the course of dis-

Received December 8, 1998; Revised March 15, 1999; Accepted March 16, 1999.

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Table 1
Categories of the Evidence Base for Conclusions on Diagnostic Methods, Including Assessment of Severity, and for Treatments of Severe Acute Pancreatitis

Category	Diagnosis or severity prediction	Treatment
A. Proven	Clear evidence of efficacy in diagnosis or severity prediction in at least two adequately powered studies	Statistically significant reduction in mortality in two or more well-designed studies, without conflicting evidence to suggest a lack of effect on mortality
B1. Probable	Evidence of efficacy in one large and/or more than one small study	Statistically significant reduction in mortality in a single, well-designed randomized study or evidence of efficacy from two or more such studies, but with conflicting evidence from other well-designed randomized studies
B2. Possible		Theoretical basis for efficacy supported by limited randomized studies or well-documented, but nonrandomized studies, or significant influence on morbidity in well-designed randomized studies
C. Consensus	Accepted practice for which supportive or contrary evidence does not exist, agreed opinion	Theoretically justified or accepted practice for which supportive or contrary evidence does not exist
Inappropriate	Diagnostic or prognostic features that have been shown to have no or poor correlation with outcome	Treatment shown to be without effect on mortality, or to be harmful, in well-conducted randomized studies

ease *(3,4)*. It is essential to evaluate the existing predictive systems and/or biochemical markers and develop new ones.

A variety of medical treatments have failed to show any benefit to patients with severe acute pancreatitis. However, the use of antibiotics or new anti-inflammatory drugs to prevent infection and reduce complications shows promise. Additionally, the role and the timing of surgical debridement remain controversial, since a number of patients still die, although they have sterile pancreatic necrosis *(5)*.

The aim of this article is to clarify the concepts of diagnosis and severity prediction in acute pancreatitis and to review the current primary management of severe acute pancreatitis (but not of its late complications, abscess and pseudocyst) to determine those aspects best supported by the published evidence.

Method

Thirty-one specialists in pancreatic disease, especially in acute pancreatitis, from a wide range of disciplines, such as anatomy, gastroenterology, internal medicine, pathology, radiology, and surgery, met in September 1997 in the Greek island Santorini to review the evidence concerning the diagnosis, the assessment of severity, and the management of acute pancreatitis, and to produce an agreed outcome statement, which would be useful for medical professionals dealing with the care of individual patients. Three groups were established to evaluate the evidence relating to diagnosis, prediction of severity, and management. Members of each group reviewed specific topics, which were discussed by the participants who graded the available evidence (Table 1), and reported back to a plenary session for open discussion and final agreement. One or two members of each group drafted sections of the final document, which was agreed to by all authors.

Modifications to the Atlanta Classification System of Acute Pancreatitis

The classification of acute pancreatitis established in Atlanta *(6)* was an important step forward in the

management of the disease, since it is clinically based, using information obtained by contrast-enhanced computed tomography (CT) and clarified definitions of the different complications. With the increased clinical use of the Atlanta system, it has become apparent to many clinical investigators that it did not provide definitive characterization for localized collections of necrotic tissues seen after necrotizing pancreatitis. Although the Atlanta system included these patients under the general heading of pancreatic necrosis, clinical differentiation of localized necrotic collections from acute pancreatic fluid collections and acute pseudocysts was often difficult. Low CT densities (<15 HU) can be seen in all three conditions and can lead to the mistaken clinical diagnosis of "pseudocysts." Moreover, if internal drainage of these "pseudocysts" is attempted, necrotic tissue may be encountered, and internal drainage can result in infection of the necrosis *(7)*. In order to distinguish these localized collections of necrotic tissues from acute pseudocysts and fluid collections, additional imaging studies are necessary. Either ultrasound or magnetic resonance pancreatography can be used to differentiate primary fluid-filled lesions (acute fluid collections or [after 4 wk] acute pseudocysts) from these collections of necrotic tissue. In clinical practice, it is wise to consider all localized collections following necrotizing pancreatitis to be localized necrosis until proven otherwise (evidence category C). The remaining definitions agreed to at Atlanta appear to be helpful in the discussion of severe acute pancreatitis.

Diagnosis

Blood Tests

Amylase and lipase are both enzymes released from the pancreas during acute pancreatitis. Plasma levels of both enzymes peak within the first 24 h of symptoms, but the half-life of amylase in plasma is shorter than that of lipase. Analysis of all published series (Table 2) shows that lipase estimation has slightly superior sensitivity and specificity and greater overall accuracy than amylase *(8–14)*. This difference becomes more marked when there is a delay in initial blood sampling. The difference in performance of these two tests, though small, is definite (evidence category A). There are no other tests on blood or plasma currently available for the diagnosis of acute pancreatitis.

Table 2
Diagnostic Sensitivity and Specificity of Different Pancreatic Enzymes in the Diagnosis of Acute Pancreatitis[a]

	Sensitivity, %	Specificity, %
Total amylase	67–100	85–98
Pancreatic amylase	67–100	83–98
Lipase	82–100	82–100
Trypsin	89–100	79–83
Elastase	97–100	79–96

[a]Data are expressed as reported ranges *(7–13)*.

Ultrasonography

It is accepted that ultrasonography plays little part in the diagnosis or staging of acute pancreatitis. This is because of the high frequency of incomplete examinations, owing to overlying bowel gas *(15,16)*. Early ultrasonography is, however, useful in the determination of gallstone etiology, by the demonstration of stones in the gallbladder, or by common bile duct dilatation *(15)* (evidence category B).

Computed Tomography (CT)

In cases of diagnostic doubt, particularly with atypical presentation when abdominal pain is not a feature or when hyperamylasaemia or hyperlipasemia have been discovered unexpectedly, pancreatic imaging by CT provides good evidence of the presence or absence of pancreatitis. Diagnostic CT signs include pancreatic swelling, peri-pancreatic infiltrates, peri-pancreatic fluid collections, and areas of nonenhancement of the pancreas *(17,18)* (evidence category C).

Outcome Statement—Diagnosis

The conclusions reached in this section are listed in Table 3.

Objective and Early Assessment of Severity

The Need

The established management of severe acute pancreatitis includes aggressive fluid replacement, oxygen supplementation as required, and full intensive care support of any failing organ or system. Early identification of severely ill patients is helpful to ensure rapid and appropriate treatment. Furthermore, recently, endoscopic sphincterotomy has

Table 3
Outcome Statements for the Diagnosis of Acute Pancreatitis

In clinical practice, it is wise to consider all localized collections following necrotizing pancreatitis to be localized necrosis until proven otherwise (evidence category C)
Lipase estimation has slightly superior sensitivity and specificity and greater overall accuracy than amylase (evidence category A)
It is accepted that ultrasonography plays little part in the diagnosis or staging of acute pancreatitis (evidence category C)
Pancreatic imaging by CT provides good evidence of the presence or absence of pancreatitis (evidence category C)

Table 4
Desirable Features of Markers of Severity

Accuracy	High sensitivity and positive predictive value
Availability	Early (<48 h) in the course of disease
	Rapid (<4 h) to be clinically useful
	Widespread: suitable for use in all hospitals receiving patients with acute pancreatitis
Reliability	Not observer-dependent
Inexpensive	

become more widely applied for the management of severe gallstone-induced acute pancreatitis (*see below*), and other specific therapies are available (e.g., antibiotic prophylaxis) or undergoing development (platelet-activating factor antagonists). It seems likely that the earlier these treatments are applied, the more effective they will be in the prevention of complications. There is therefore a need for an early objective measure of severity (evidence category C). Severity markers should show most of the features described in Table 4.

In order to make comparisons of different therapeutic series, it is important to clarify the number of patients with a predicted severe attack, based on prognostic factors or scores, and the actual severity, as defined by the presence of a complication. Further, it is helpful to define the number of patients with organ failure at admission, since this value may vary, and gives an indication of the severity of the disease in the population studied.

Clinical Features

Clinical examination in the first 24 h of admission is unreliable. After 48 h, clinical assessment is almost as accurate as the Ranson or Glasgow Scores *(19,20)* (evidence category A). However, 48 h after admission is probably too late to begin specific therapy.

Body wall bruising (Grey Turner's and Cullen's signs) is associated with a particularly severe outcome: one paper documented a 37% mortality rate when this sign was present *(21)*. However, bruising is seen relatively rarely, which limits its usefulness. Furthermore, bruising often appears 48–72 h after onset of symptoms. There is therefore a need to define other, objective measures of severity, which can be applied early in the course of the disease.

Multiple Factor Scoring Systems

In the 1970s, two systems were developed to assist in the categorization of patients with acute pancreatitis. The system proposed by Ranson was complicated by the requirement for two separate systems dependent on alcohol or gallstone etiology *(22,23)*. The Glasgow System, and its subsequent modification *(24–26)* works well in all types of pancreatitis. However, both these systems require 48 h from admission for full assessment.

There have been two comparisons of the two pancreatitis-specific systems described above, with other multiple factor scoring systems. Larvin and McMahon *(27)* compared them with the acute physiology and chronic health evaluation (APACHE II) and the simplified acute physiology score (SAPS), and found that at 48 h, APACHE II worked at least as well as the Ranson or Glasgow Scores, and was superior to the SAPS. However, the advantage of APACHE II was that prediction using this system at 24 h was as effective as the other scores at 48 h. The superiority and earlier assessment with APACHE II have been confirmed *(28)*. If a multiple factor scoring system is to be used, the best choice at present appears to be APACHE II calculated at 24 h (evidence category A).

Individual or Group Scores?

The scoring systems studied to date have all been designed to categorize levels of risk in populations.

The main benefit of this is that it allows comparison of different series with an objective measure of severity. However, for an individual, there is an in-built, often unquantified inaccuracy in the allocation to the category of either "predicted severe" or "predicted mild." Of greater clinical utility would be a prognostic score, which used the data acquired by the multiple factor scoring systems to calculate the individual's risk (probability) of development of a complication. This individual value could then be used for individual treatment decisions. No such system is currently available.

Single Factor Risk Assessment

Currently the best prediction of an individual's risk of a complication lies in the use of a number of factors *(44)*, which have been shown independently to predict a severe outcome. These include clinical features, markers of pancreatic injury, and markers of the inflammatory response. Some of these factors have been tested in clinical use, but the majority have been studied only in a research setting. There is urgent need for comparative studies of clinical, pancreatic, and inflammatory markers to determine their relative clinical utility (evidence category C).

Predictive Clinical Observations

The value of body wall ecchymosis as a specific marker of complications and death has been noted above *(21)* (evidence category B). In four large studies, obesity has been confirmed as a risk factor for serious complications, and in two of these, it was a useful marker of a fatal outcome *(29–32)*. Obesity can be characterized objectively by calculation of body mass index (BMI) (weight [kg]/height^2[*M*] > 30). There is a suggestion that intermediate obesity (BMI 25–30) predicts a lesser, but nevertheless increased risk compared with normal body habitus *(29)*. Obesity predicts a severe outcome independently of age and acute physiology score (the two major components of APACHE II). Obesity, as shown by a BMI > 30 is a reliable predictor of a severe outcome (evidence category A).

A number of studies have shown that a chest radiograph within 24 h of admission can be useful for the prediction of complications. Pulmonary infiltrates or lung field opacities are, however, too observer-dependent to be widely reliable. Two studies have indicated a significant association between pleural effusion on the early chest X-ray and subsequent complications or fatal outcome. Although there is some increased risk with a right pleural effusion, the predictive value is maximal with left-sided or bilateral effusions *(33–35)* (evidence category B).

One study has shown additional predictive value from the observation of plasma creatinine levels in excess of twice the upper limit of normal *(33)*. This finding requires confirmation (evidence category B).

Computed Tomography (CT)

It is generally accepted that evidence on CT of areas of hypoperfusion (nonenhancement) correlates well with pancreatic necrosis. The Atlanta symposium *(6)* recognized areas of nonenhancement >30% of the pancreas or >3 cm diameter as diagnostic of necrosis. Consequently, this CT sign correlates with other complications of acute pancreatitis.

It seems likely that the appearances of necrosis become more clearly defined during the first 96 h after admission. There are no published data to support the routine use of CT within the first 24 h of admission, to diagnose necrosis or to predict severity. Indeed, it seems likely that such a policy would lack sensitivity.

CT is useful for the diagnosis of pancreatic necrosis, with close to 100% sensitivity between 4 and 10 days *(36–44)* (evidence category A). There are a lack of data on the diagnostic and predictive value of CT using modern spiral scanners. Further studies are desirable to determine the value of early CT in prediction of complications other than necrosis, using modern scanners and protocols (evidence category C).

Markers of Pancreatic Injury

Plasma levels of the pancreatic enzymes amylase and lipase have no value in prediction of severity, probably related to the rapid fall off after the early peak *(22,26)* (evidence category A). Measurement of serum trypsinogen may be of predictive value, but is not currently available in any clinically useful assay *(45)*.

Phospholipase A_2, produced in the pancreas and also produced by neutrophil activation, is a good early marker of severe pancreatitis, confirmed in several studies *(46–48)*. (evidence category A). However, the assay is cumbersome and is not currently available in a clinically useful form.

Pancreatitis-associated protein (PAP) is synthesized in response to pancreatic injury and is expressed

in acute pancreatitis. However, it appears to have no role in the assessment of severity *(49)* (evidence category B). These markers of pancreatic injury have no clinical application at present (evidence category C).

Activation Peptides

Trypsinogen activation peptide has been known for a decade to be a marker of severe pancreatitis. Raised plasma levels and raised urinary levels of trypsin activation peptide (TAP) correlate well with severity *(50)*. However, it has taken many years to develop a clinically applicable assay, and the small TAP molecule is present in very low concentrations in urine. It is rapidly cleared from plasma. Although a recent publication indicates that a recently introduced test may be of value *(51)*, further clinical data are awaited. If a reliable assay can be developed, TAP is a useful predictor of severity (evidence category A).

The activation peptide of 1-prophospholipase A_2 has been proposed as an additional indicator of severity *(52)*. Further data are required to allow evaluation of this claim.

Carboxypeptidase activation peptide (CAPAP) is also released from the pancreas in severe acute pancreatitis. This molecule is 10 times larger than TAP and is robust in blood and urine, where it is found in large quantities in severe pancreatitis. Preliminary data suggest that this may be a useful marker of severe pancreatitis, but confirmation is awaited *(53,54)* (evidence category B) Activation peptides TAP and CAPAP show great promise as markers of severity (evidence category A/B). Further development is required for these assays to be clinically useful.

Markers of Immune Activation

A number of inflammatory mediators and markers have been shown to be significantly associated with severe outcome in acute pancreatitis (Table 5). Interleukin (IL) 8 *(55,56)* and IL-6 *(55–60)* have been shown to peak within the first 24 h after onset of symptoms, and to provide good discrimination between mild and severe acute pancreatitis. Rapid dipstick methods of analysis for IL-8 *(60)* are understood to be nearing the final stages of development, but these have not been tested in clinical practice. The anti-inflammatory cytokine IL-10 has been shown to reduce the inflammatory response in experimental pancreatitis. Clinical evidence suggests that this may also occur in human disease, and that higher levels of IL-10 are found in the serum of patients with mild disease *(61)*. Although of interest in understanding the pathophysiology of the disease, the relevance of this observation for prediction of severity remains to be established.

Table 5
Immune Markers Elevated in Severe Acute Pancreatitis

	Peak	Clinically useful
IL-8	12–24 h	<24–72 h
IL-6	24 h	24–48 h?
PMN elastase	12–24 h	Up to 48 h
CRP	3–4 d	After 48 h

Tumor necrosis factor (TNF) is released in bursts in severe acute pancreatitis, and elevated levels may be detected in this condition *(62,63)*. However, the variable and phasic release of TNF make it unsuitable for use as a predictor of a severe attack *(64)*. de Beaux et al. *(65)* showed clear separation of mild, severe, and fatal attacks by measurement of the serum concentration of soluble TNF receptors, and Schölmerich's group *(66)* has reported preliminary data confirming that TNF receptor estimations may be of value in the early prediction of severity. Development of this assay for clinical use is awaited.

Polymorphonuclear (PMN) elastase has been shown to have a good predictive value for severe acute pancreatitis *(66–68)*. However, there have been some difficulties with the assay system, which is still not suitable for routine use. An improved assay is likely to be available in the near future, but this will require testing in clinical practice.

A number of markers are suitable for the urgent assessment of severity including IL-8 and IL-6 (evidence category A), TNF soluble receptors (evidence category B), and PMN elastase (evidence category A). Because of their likely usefulness, development of rapid tests suitable for clinical application is urgently required (evidence category C).

C-reactive protein is a widely available assay that is cheap to perform and gives rapid results. However, it only rises after the early peaks of the inflammatory mediators. CRP becomes a good discriminator of severe and mild disease 48 h after onset of symptoms. A cutoff level of 150 mg/L is now accepted *(56,57,59,65,66)* (evidence category A).

Table 6
Suggested Cutoff Values
for Proven Markers of Severity

Obesity	BMI > 30
Chest radiography	Left/bilateral effusion
APACHE II	≥6
APACHE O[a]	≥6
CRP	>150 mg/L

[a]APACHE II plus 1 point BMI 25–30, 2 points BMI > 30.

Outcome Statement—Assessment of Severity

The conclusions of this section are listed in Tables 6 and 7. Attention is drawn particularly to the value of simple clinical markers of severity, such as obesity and pleural effusion, and to the usefulness of APACHE II within 24 h of admission to hospital.

Prevention of Complications and Conservative Management

Previous failure to identify therapeutic agents that unquestionably influence the course of acute pancreatitis has led to an attitude of nihilism. However, new candidates for preventative treatments are emerging, which hold much greater promise. This emphasizes the need for early diagnosis and early assessment of severity. Severe pancreatitis is a complex and multifaceted disease, which places great demands on the skill, experience, and endurance of those who manage it.

The management of acute pancreatitis must start as soon as possible with abundant fluid replacement and supportive care. Early restoration of circulating volume and arterial oxygen tension to normal should reduce the risk of extensive necrosis and other complications (evidence category C).

A specialist center for the management of severe acute pancreatitis should meet the following criteria:

- A large general hospital with a full range of principal medical and surgical specialities.
- Surgeons, physicians, radiologists, intensivists, pathologists, and microbiologists with specialist skill and experience in the management of severe acute pancreatitis.
- CT available 24 h/d.
- Experienced endoscopists with endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy available daily as a routine service, and at weekends and during holidays as an emergency service.

These criteria are broadly similar to those proposed in the UK guidelines for the management of acute pancreatitis *(69)*. It is recommended that wherever possible, patients with severe acute pancreatitis be transferred, as rapidly as possible, to recognized specialist centers (evidence category C).

Efficacy of Treatment for Acute Pancreatitis

Most patients with acute pancreatitis suffer little or no sequelae of the attack if it has been managed successfully. Accordingly, mortality rate is by far the most important yardstick by which to gauge efficacy, and treatment cannot be regarded as successful in this condition unless mortality rates can be reduced. Nevertheless, the impact of treatment on complications may be a helpful end point by which to gauge the potential value of treatments in studies that lack the power to demonstrate an influence on mortality rate.

Antibiotics

The value of prophylactic antibiotics in severe pancreatitis has been continuously debated on for more than half a century *(70)*. Results from recent controlled clinical trials suggest that there probably is a role for antibiotics in the prevention of complications and probably for the reduction of mortality rates *(70–76)*. There is also a large body of experimental evidence to support this conclusion, and the observations that Gram-negative bacteria are the most important with regard to prognosis and that they originate from the gut *(77–79)*.

All the recent studies, apart from one *(72)*, showed a significant reduction of infected necrosis and pancreatic abscess in the treated patients when compared to controls. Mortality rate was reduced only in two trials *(72,75)*. In particular, systemic antibiotics with selective gut decontamination *(75)* reduced the late mortality (>2 wk from disease onset) as a secondary effect to a decrease of Gram-negative infection.

Regardless of the criticisms that may be made of each of these clinical studies, taken together, they indicate that prophylactic antibacterial treatment is strongly recommended in severe pancreatitis (evidence category B1). However, it remains to be decided which drugs should be used, and whether they should be given alone or in combination, or together with gut decontamination. There is no evidence to help decide when to start prophylactic treat-

Table 7
Features That Predict a Severe Attack of Acute Pancreatitis

There is a need for an early objective measure of severity (evidence category C)
Clinical examination in the first 24 h of admission is unreliable (evidence category A)
If a multiple-factor scoring system is to be used, the best choice at present appears to be APACHE II calculated at 24 h (evidence category A)
There is an urgent need for comparative studies of clinical, pancreatic and inflammatory markers to determine their relative clinical utility (evidence category C)
Obesity as shown by a BMI > 30 is a reliable predictor of a severe outcome (evidence category A)
Two studies have indicated significant association between pleural effusion on the early chest X-ray and subsequent complications or fatal outcome (evidence category B)
Evidence on CT of areas of hypoperfusion (nonenhancement) correlates well with pancreatic necrosis (evidence category C)
CT is useful for the diagnosis of pancreatic necrosis, with close to 100% sensitivity between 4 and 10 d (evidence category A)
Further studies are desirable to determine the value of early CT in prediction of complications other than necrosis, using modern scanners and protocols (evidence category C)
Plasma levels of the pancreatic enzymes amylase and lipase have no value in prediction of severity, probably related to the rapid fall off after the early peak *(23,27)* (evidence category A)
Phospholipase A_2 is a good early marker of severe pancreatitis (evidence category A); other markers of pancreatic injury have no clinical application at present (evidence category C)
Activation peptides TAP and CAPAP show great promise as markers of severity (evidence category A/B); further development is required for these assays to be clinically useful
A number of markers are suitable for the urgent assessment of severity including IL-8 and IL-6 (evidence category A), TNF soluble receptors (evidence category B), and PMN elastase (evidence category A); because of their likely usefulness, development of rapid tests suitable for clinical application is urgently required (evidence category C)
CRP becomes a good discriminator of severe and mild disease 48 h after onset of symptoms; a cutoff level of 150 mg/L is now accepted (evidence category A)

ment or how long to continue therapy. Most clinicians now use antibiotics, alone or with selective digestive decontamination for the management of severe pancreatitis. Appropriate antibiotics are those that are active against a wide variety of organisms, in particular Gram-negative pathogens. Antibacterial therapy should be commenced as early as possible after the identification of a severe attack (evidence category C).

Endoscopic Sphincterotomy

Over the last 10 years, there has been an increasing body of evidence supporting the rationale for endoscopic treatment (endoscopic sphincterotomy [ES] and related procedures) in patients with acute biliary pancreatitis (ABP) *(80)*. To date, there have been four randomized controlled trials of urgent ERCP and ES in ABP, in which ERCP was performed within 24 h *(81)* or within 72 h *(82–84)* from admission.

Three studies showed a significant reduction of complications and reduction of mortality rate in those patients undergoing endoscopic treatment in comparison with those conventionally treated: the British *(82)* and Hong Kong studies *(81)* for patients with severe forms of ABP, the Polish study *(83)*, at present available only in abstract form, for patients with predicted severe and mild pancreatitis. The German trial *(84)* did not show benefit of early ERCP and ES in gallstone pancreatitis, but this study excluded (and offered ERCP to all) patients with evidence of cholangitis or jaundice. These patients are most likely to have persisting bile duct stones and are most likely to benefit from endoscopic treatment.

Urgent endoscopic treatment is recommended in patients with severe forms of ABP and abnormal

liver function, which includes patients with cholangitis. The timing of ERCP and ES should be as early as possible and no longer than 72 h from hospital admission (evidence category B1).

Endoscopic sphincterotomy during the early stages of acute biliary pancreatitis should be carried out only in specialist centers (evidence category C). Appropriate circumstances for the consideration of urgent endoscopic sphincterotomy are:

- Severe pancreatitis (presence of organ failure or predicted severe disease).
- Symptoms of < 72 h duration.
- Gallstones demonstrated by ultrasonography, alanine transaminase or aspartate transaminase levels of at least of twice the upper limit of normal, or jaundice or bilirubin level equal to or greater than twice the upper limit of normal.
- It is recommended that ERCP and ES be carried out as part of the routine daily service by an experienced endoscopist as soon as possible after the need for ES is identified.

Enteral Nutrition

Three relatively small randomized studies have suggested a reduction of complications and possibly mortality from the early institution of enteral feeding delivered beyond the ligament of Treitz *(85,86)*. This is associated with a reduction in the markers of immune stimulation in patients receiving enteral nutrition *(87)*. Enteral feeding, started early in the course of severe acute pancreatitis, is safe, theoretically attractive, and probably reduces the risk of complications (evidence category B2).

Experience with nutritional support is needed, and when enteral nutrition is administered in the early stages of severe acute pancreatitis, appropriate safeguards should be undertaken to ensure jejunal placement of the tube and to avoid vomiting and aspiration if ileus is present. There may be an important role for enteral nutrition in the postoperative management of patients undergoing operations for severe acute pancreatitis (evidence category C).

Inhibitors of PAF

Evidence of probable efficacy of lexipafant (a potent inhibitor of PAF) is based on two small randomized studies *(88,89)*. In both studies, a significant reduction of organ failure was demonstrated in patients with predicted severe acute pancreatitis who received lexipafant treatment within 72 h of the onset of symptoms. Another large multicenter randomized study has been completed, but is published only in abstract form *(90)*. This suggests that mortality rates may be reduced if treatment is started within 48 h of onset of symptoms. A further large randomized multicenter study is in progress. Lexipafant treatment within 48 h of onset of symptoms can reduce complications, especially organ failure, and possibly mortality rate, in patients with predicted severe acute pancreatitis (evidence category B2). Lexipafant cannot be recommended for the treatment of acute pancreatitis until the current multicenter study has been completed.

Antiprotease and Antisecretory Drugs

Randomized studies have failed to show significant impact of these agents on mortality rates. A wide variety of antiprotease and antisecretory agents, including aprotinin, glucagon, anticholinergics, and fresh frozen plasma, have no effect in severe acute pancreatitis *(69)* (evidence category A).

Gabexate mesilate showed negative results at 90 d observation in a German trial *(91)*, whereas positive results on early complication rates (<2 wk) have been reported in an Italian comparison against aprotinin *(92)* and in a metaanalysis *(93)*. Somatostatin showed beneficial effects only in a meta-analysis *(94)*. Recently, in two randomized trials (from UK and Germany), octreotide failed to show any benefit on mortality rate and complications *(95,96)*. Modern antiprotease therapy (gabexate mesilate) and antisecretory therapy (somatostatin, octreotide) have no effect on mortality rates (evidence category A). Gabexate and somatostatin may have some effect on reducing complications, but the evidence is weak (evidence category B2).

Outcome Statement—Prevention of Complications

The conclusions of this section are listed in Table 8.

Recommendations for Further Trials of Treatment

A further randomized trial of lexipafant is being carried out at the present time. There is a need for large multicenter, well-designed randomized trials of enteral nutritional support and antibiotic therapy or selective digestive decontamination. In view of conflicting evidence concerning the role of ES, a further randomized study with careful patient selection on a multicenter basis is suggested.

Table 8
Outcome Statement for Preventative and Nonoperative Treatment of Complications

Early restoration of circulating volume and arterial oxygen tension to normal will reduce the risk of extensive necrosis and other complications (evidence category C)
It is recommended that wherever possible, patients with severe acute pancreatitis be transferred, as rapidly as possible, to recognized specialist centers (evidence category C)
Prophylactic antibacterial treatment is strongly recommended in severe pancreatitis (evidence category A)
Appropriate antibiotics are those that are active against a wide variety of organisms, in particular Gram-negative pathogens; antibacterial therapy should be commenced as early as possible after the identification of a severe attack (evidence category C)
Urgent endoscopic treatment is recommended in patients with severe forms of ABP and abnormal liver function, which includes patients with cholangitis. The timing of ERCP and ES should be as early as possible and no longer than 72 h from hospital admission (evidence category B1)
Endoscopic sphincterotomy during the early stages of acute biliary pancreatitis should be carried out only in specialist centers (evidence category C)
Enteral feeding, started early in the course of severe acute pancreatitis, is safe, theoretically attractive, and probably reduces the risk of complications (evidence category B1)
There may be an important role for enteral nutrition in the postoperative management of patients undergoing operations for severe acute pancreatitis (evidence category C)
Lexipafant treatment within 48 h of onset of symptoms can reduce complications, especially organ failure, and possibly mortality rate in patients with predicted severe acute pancreatitis (evidence category B2)
A wide variety of antiprotease and antisecretory agents, including aprotinin, glucagon, anticholinergics, and fresh frozen plasma, have no effect in severe acute pancreatitis (evidence category A)
Modern antiprotease therapy (gabexate mesilate) and antisecretory therapy (somatostatin, octreotide) have no effect on mortality rates (evidence category A)
Gabexate and somatostatin may have some effect to reduce complications, but the evidence is weak (evidence category B2)

Prevention of Acute Pancreatitis

The principal opportunity for the prevention of acute pancreatitis is in patients undergoing ERCP. Antienzyme preparations may have a role, despite their lack of efficacy on the mortality in the management of established pancreatitis. One well-designed randomized study showed an influence of Gabexate mesilate on mortality *(97)* (evidence category B1). It is suggested that further randomized studies be carried out. In view of the desirability of administration of prophylactic agents prior to the commencement of ERCP, further information is required about the selection process for high-risk patients.

Surgical Treatment

Concepts regarding the nature of appropriate surgical intervention in acute pancreatitis have varied widely in the last decade. The pendulum has swung from early major intervention to limited intervention and intervention at a later phase with specific criteria governing the timing of surgical therapy *(98–100)*. Careful but nonrandomized assessment of the outcome of early intervention has led to the conclusion that the results have failed to support this approach, and some authors specifically attempt to delay surgical intervention *(101–103)*. In late-phase intervention, the surgical thrust is focused on dealing with specific complications, such as abscess and necrosis *(100–103)*.

Given that the biology of acute pancreatitis is still poorly understood, the rationale for surgical intervention is not easy to define. Moreover, the surgical intervention itself is not always based on clear guidelines to which the clinician can refer; indeed, other guidelines avoid discussion of surgical management altogether *(69)*. This is owing largely to (1) the intrin-

sic complexity of pancreatitis in its early toxic stages and (2) the difficulty in understanding the relevant information reported in the literature, which is incomplete and based on confused terminology. The terminology defined in the Atlanta criteria *(6)* should be used (with the modification suggested above) to clarify discussion of the management of local complications.

In some cases, an early laparotomy may be required, when the diagnosis is uncertain and CT or magnetic resonance (MR) imaging is not avalaible, and an operation is needed to establish the pathology of the intra-abdominal event (evidence category C). Early laparotomy and exposure of the pancreas may be helpful in a patient with rapid progression of multiple-organ failure despite full intensive care (evidence category C).

Undoubtedly, the development of pancreatic parenchymal and/or extrapancreatic necrosis is the critical feature determining the prognosis of and the need for surgery in acute pancreatitis *(100,103,104)* (evidence category A).

The determination of the presence of pancreatic necrosis by enhanced CT is still regarded as the appropriate investigative modality necessary for determining therapeutic intervention. CT can also be used as a "road map" for identifying retrocolic and intramesenteric extensions of necrosis *(36,38–42)*. As noted above, this may be delayed for 7–10 d to help decide the need for surgical intervention after the early acute inflammatory phase, or when operation is indicated on clinical grounds. Peritoneal aspiration with the fluid subjected to a "smell test" and then immediate Gram stain can also be very valuable in facilitating the decision of the appropriate treatment *(44)*.

The available data do not support a general operative policy toward patients with sterile necrosis (evidence category A). The principal reasons for this are twofold: first, patients with sterile necrosis may be managed nonoperatively *(101,102)* and a significant improvement in mortality has not been demonstrated following necrosectomy in patients with sterile necrosis *(105–107)*, and second, operative intervention may convert sterile necrosis to secondarily infected pancreatic necrosis, with attendant doubling of the mortality rate *(100,107,108)*. Nevertheless, subgroups of patients with sterile necrosis might benefit from necrosectomy (evidence category C):

1. Patients continuing to deteriorate from systemic inflammatory response syndrome (SIRS) despite maximal support positive end-expiratory pressure ([PEEP] > 15 with progressive deoxygenation; pulmonary capillary wedge pressure [PCWP] > 20 with hypotension and oliguria).
2. Patients continuing to exhibit a "septic" picture 10 d or more after onset.
3. Recurrent abdominal pain and hyperamylasemia following attempts at oral feeding 3–4 wk after onset (many if not all of these patients will be found to have pancreatic ductal disruption).

The difficult to define, but important criterion of clinical judgment appears to be at least as important as the establishment of the level or rate of deterioration, particularly in cases (1) and (2).

Infected Necrosis

Special attention was given to the necessity for fine needle aspiration (FNA) as the appropriate method for determining whether pancreatic necrosis is infected or not. Apart from surgical necrosectomy, FNA is the only reliable test to diagnose infected necrosis *(109–112)* (evidence category A). Despite concerns about possible introduction of infection or dissemination of organisms by intestinal puncture, this need not be a problem *(110,111)* (evidence category B).

Unroofing of all retroperitoneal collections and thorough debridement are necessary in the management of infected necrosis *(100,102,103)* (evidence category A). However, there is no general agreement on the type of operation that should be used. The UK guidelines avoid this difficult area altogether *(69)*. Necrosectomy with continuous closed lavage, debridement with open packing, with or without secondary closure, and necrosectomy and drainage with planned reoperation all have similar results *(100,102–104,113–117)*. No specific criteria for the determination of the ideal technique are available. The choice of surgical technique can be based on clinically derived experience (evidence category B2).

Outcome Statement—Surgical Treatment of Pancreatic Necrosis

The principles that govern the decision to operate and the choice of operation are shown in Table 9.

Table 9
Surgical Treatment for Severe Acute Pancreatitis and Pancreatic Necrosis

In some cases, an early laparotomy may be required, when the diagnosis is uncertain and an operation is needed to establish the pathology of the intra-abdominal event (evidence category C)
Early laparotomy and exposure of the pancreas may be helpful in a patient with rapid progression of multiple-organ failure despite full intensive care (evidence category C)
The development of pancreatic parenchymal and/or extrapancreatic necrosis is the critical feature determining the prognosis of and the need for surgery in acute pancreatitis (evidence category A)
The data available do not support a general operative policy toward patients with sterile necrosis (evidence category A)
It is possible that subgroups of patients with sterile necrosis might benefit from necrosectomy (evidence category C)
FNA is the only reliable test to diagnose infected necrosis (evidence category A); introduction of infection or dissemination of organisms by intestinal puncture during FNA need not be a problem (evidence category B)
Unroofing of all retroperitoneal collections and thorough debridement are necessary in the management of infected necrosis (evidence category A)
No specific criteria for the determination of the ideal technique are available; the choice of surgical technique can be based on clinically derived experience (evidence category B2)

Areas for Future Investigation

Continued re-evaluation of the indications for surgery in sterile necrotizing pancreatitis will be necessary. In particular, it will be important to determine whether or not necrosectomy confers any survival benefit to patients with progressive organ failure despite maximum support. At the moment, no single study exists that compares operative vs nonoperative therapy in this challenging group. Resolution of technical controversies surrounding surgical drainage options awaits creation of a multi-institutional study.

Conclusions

This article considers the diagnosis, assessment of severity, and management of patients with severe acute pancreatitis. Previous consensus on definitions *(6)* remains broadly acceptable; clarification was required of the terminology and significance of acute fluid collections. There have been several recent developments in the assessment of severity and in the prevention of complications, which are barely touched on in the UK guidelines *(69)*. Although published in 1998, preparation of that document began in 1995, and updating has been required in these areas. Furthermore, the present document makes clear statements about surgical management of pancreatic and peripancreatic necrosis, which were previously lacking.

Acknowledgments

This consensus article is the result of the combined efforts of the following participants: Åke Andrén-Sandberg, Lund, Sweden, Claudio Bassi, Verona, Italy,* Dale Bockman, Augusta, GA, Edward Bradley, Buffalo, NY,* Giorgio Cavallini, Verona-Italy, Christos Dervenis, Athens-Greece,* Eugene DiMagno, Rochester, NY, E. Dominguez-Munoz, Compostella, Spain, Gyula Farkas, Szeged-Hungary, Efthimios Hatzitheoklitos, Thessaloniki, Greece, Ingemar Ihse, Lund, Sweden, Clem Imrie, Glasgow, UK,* Colin Johnson, Southampton, UK,* John Karagiannis, Athens, Greece, Andrew Kingsnorth, Plymouth, UK, Michael Larvin, Leeds, UK, Ernest Luiten, Geldrop, Natherlands, Colin McKay, Glasgow, UK, Michael McMahon, Leeds, UK,* Irvin Modlin, New Haven, CT,* Raffaele Pezzilli, Bologna, Italy, Carlo Procacci, Verona, Italy, Jurgen Scholmerich, Regensburg, Germany, Michael Steer, Boston, MA, Christophoros Stoupis, Athens, Greece, Giorgio Talamini, Verona, Italy, Tibor Tihanyi, Budapest, Hungary, Waldemar Uhl, Bern, Switzerland, and Generoso Uomo, Naples, Italy. Financial support for this symposium was provided by the following companies: British Biotech Ltd., Novartis Hellas, and Solvay Pharma.

**Authors*

References

1 Wilson C, Imrie CW. Deaths from acute pancreatitis. Why do we miss the diagnosis so frequently? *Int J Pancreatol* 1988; 3: 273–282.

2 Lankish PG. Undetected fatal acute pancreatitis; why is the disease so frequently overlooked? *Am J Gastroenterol* 1991; 86: 322–326.

3 Williamson RCN. Early assessment of severity of acute pancreatitis. *Gut* 1984; 25: 1331–1339.

4 Glazer G, Dudley HAF. The surgical managment of acute pancreatitis. *Ann R Coll Surg Engl* 1987; 69: 249,250.

5 Buchler M, Uhl W, Beger HG. Complications of acute pancreatitis and their management. *Curr Opinion Gen Surg* 1993; 282–286.

6 Bradley EL. A clinically based classification system for acute pancreatitis: Summary of the Atlanta symposium. *Arch Surg* 1993; 128: 586–590.

7 Hariri M, Slivka A, Carr-locke DL, Banks PA. Pseudocyst drainage predisposes to infection when pancreatic necrosis is undiagnosed. *Am J Gastroenterol* 1994, 89: 1781–1794.

8 Buchler M, Uhl W, Malfertheiner P. Elastase 1 in acute pancreatitis, in *Acute Pancreatitis*, Beger HG, Buchler M (eds.), Springer-Verlag Berlin, Heidelberg, 1987; pp. 110–117.

9 Saccetti L, Cavalcanti E, Cerasuolo S, et al. Evaluation of pancreatic amylase immunoassay in acute pancreatitis. *Clin Chim Acta* 1989; 183: 95–100.

10 Bowen M, Cooper EH, McMahon MJ. The diagnosis of acute pancreatitis:enhanced sensitivity from an ELISA assay of lipase. *Biomed Pharmacother* 1983; 37: 395–398.

11 Gullo L, Ventrucci M, Pezzilli R, Plate L, Naldoni P. Diagnostic value of serum elastase 1 in pancreatic disease. *Br J Surg* 1987; 74: 44–47.

12 Ventrucci M, Pezzilli R, Gullo L, Plate L, Sprovieri G, Barbara L. Role of pancreatic enzyme assays in diagnosis of pancreatic disease. *Dig Dis Sci* 1989; 34: 39–45.

13 Kazmierczak SC, Catron PG, VanLente F. Diagnostic accuracy of pancreatic enzymes evaluated by used of multivariate data analysis. *Clin Chem* 1993; 39: 1960–1965.

14 Dominguez-Munoz JE, Malfertheiner P. Diagnosis of acute pancreatitis, in *Advances in Pancreatic Disease*, Dervenis, CG (ed.), Thieme-Verlag Stuttgart, New York, 1996; pp. 124–131.

15 McKay AJ, Imrie CW, O'Neill J, Duncan JG. Is an early ultrasound scan of value in acute pancreatitis? *Br J Surg* 1982; 69: 369–372.

16 Moosa AR. The impact of computer tomography and ultrasound on surgical practice. *Bull Am Coll Surg* 1982; 67: 10–4.

17 Freeny PC. Radiology of acute pancreatitis, in *Acute Pancreatitis*, Glazer G, Ranson JHC (eds.), Balliere Tindall, London 1988; pp. 275–302.

18 Balthazar EJ. CT diagnosis and staging of acute pancreatitis. *Radiol Clin North Am* 1989; 27: 19–37.

19 McMahon MJ, Playforth MJ, Pickford IR. A comparative study of methods for the prediction of severity of attacks of acute pancreatitis. *Br J Surg* 1980; 69: 29–32.

20 Corfield AP, Cooper MJ, Williamson RCN, et al. Prediction of severity in acute pancreatitis: a prospective comparison of three prognostic indices. *Lancet* 1985; ii: 403–406.

21 Dickson AP, Imrie CW. The incidence and prognosis of body wall ecchymosis in acute pancreatitis. *Surg Gynaecol Obstet* 1984; 159: 343–347.

22 Ranson JHC, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. *Surg Gynaecol Obstet* 1974; 139: 69–81.

23 Ranson JHC. The timing of biliary surgery in acute pancreatitis. *Ann Surg* 1979; 189: 654–662.

24 Imrie CW, Benjamin IS, McKay AJ, McKenzie I, O'Neill J, Blumgart LH. A single centre double blind trial of Trasylol therapy in primary acute pancreatitis. *Br J Surg* 1978; 65: 337–341.

25 Osbourne DH, Imrie CW, Carter DC. Biliary surgery in the same admission for gallstone associated acute pancreatitis. *Br J Surg* 1981; 68: 758–761.

26 Blamey SL, Imrie CW, O'Neill J, Gilmour WM, Carter DC. Prognostic factors in acute pancreatitis. *Gut* 1984; 25: 1340–1346.

27 Larvin M, McMahon MJ. APACHE-II score for assessment and monitoring of acute pancreatitis. *Lancet* 1989; 11: 201–205.

28 Wilson C, Heath DI, Imrie CW. Prediction of outcome in acute pancreatitis: a comparative study of APACHE-II clinical assessment and multiple factor scoring systems. *Br J Surg* 1990; 77: 1260–1264.

29 Toh SKC, Walters J, Johnson CD. APACHE-O a new predictor of severity in acute pancreatitis. *Gut* 1996; 38 (Suppl 1): A35.

30 Lankisch PG, Schirren CA. Increased body weight as a prognostic parameter for complications in the course of acute pancreatitis. *Pancreas* 1990; 5: 626–629.

31 Porter KA, Banks PA. Obesity as a predictor of severity in acute pancreatitis. *Int J Pancreatol* 1991; 10: 247–252.

32 Funnell IC, Bornman PC, Weakley SP, Terblanche J, Marks IN. Obesity: an important prognostic factor in acute pancreatitis. *Br J Surg* 1993; 80: 484–486.

33 Talamini G, Bassi C, Falconi M, et al. Risk of death from acute pancreatitis. *Int J Pancreatol* 1996; 19: 15–24.

34 Pezzilli R, Billi P, Baraket P. Peripheral leukocyte count and chest X-ray in the early assessment of the severity of acute pancreatitis *Digestion* 1996; 57: 25–32.

35 Talamini G,Uomo G, Pezzilli R, et al. Renal function and chest X-rays in the assessment of 539 acute pancreatitis patients. *Gut* 1997; 41: A136.

36 Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH. Acute pancreatitis: value of CT in establishing a diagnosis. *Radiology* 1990; 174: 331–336.

37 Vesentini S, Bassi C, Talamini G, Cavalini G, Campedilli A, Pederzoli P. Prospective comparison of C-reactive protein level, Ranson score and contrast enhanced computed tomography in the prediction of septic complications of acute pancreaitis. *Br J Surg* 1993; 80: 755–757.

38 Kemppainen E, Sainio V, Haapiainen R, Kivisaari L, Kivilaakso E, Puolakkainen P. Early localisation of necrosis by

contrast enhanced computed tomography can predict outcome in severe acute pancreatitis. *Br J Surg* 1996; 83: 924–929.
39 Moulton JS. The radiologic assessment of acute pancreatitis and its complications. *Pancreas* 1991; 6(Suppl 1): 13–22.
40 Nuutinen, P Kivisaari L, Schroder T. Contrast enhanced computed tomography and microangiography of the pancreas in acute human hemorrhagic/necrotizing pancreatitis. *Pancreas* 1988; 3: 53–60.
41 London NJ, Leese T, Lavelle JM, et al. Rapid-bolus contrast enhanced dynamic computed tomography in acute pancreatitis: a prospective study. *Br J Surg* 1991; 78: 1452–1456.
42 Bradley EL, Murphy F, Ferguson C. Prediction of pancreatic necrosis by dynamic pancreatography. *Ann Surg* 1989; 210: 495–503.
43 Larvin M, Chalmers AG, McMahon MJ. Dynamic contrast enhanced CT: A precise technique for the indetification of pancreatic necrosis. *Br Med J* 1990; 300: 1425–1428.
44 Pickford IR, Blackett RI, McMahon MJ. Early assessment of severity using peritoneal lavage *Br Med J* 1977; ii: 1377–1379.
45 Sainio V, Puolakkainen P, Kempainnen E, et al. Serum trypsinogen-2 in the prediction of outcome in acute necrotizing pancreatitis. *Scand J Gastroenterol* 1996; 31: 818–824.
46 Nevalainen TJ. The role of phospholipase A in acute pancreatitis. *Scand J Gastroenterol* 1980; 15: 641–650.
47 Büchler M, Malfertheiner P, Schädlich H, Nevalainen TJ, Freiss H, Beger HG. Role of phospholipase A_2 in human acute pancreatitis.. *Gastroenterology* 1989; 97: 1521–1526.
48 Bird NC, Goodman AJ, Johnson AG. Serum phospholipase A_2 activity in acute pancreatitis: an early guide to severity. *Br J Surg* 1989; 76: 731,732.
49 Pezzilli R, Billi P, Migliori M, Gullo L. Clinical value of pancreatitis associated protein in acute pancreatitis. *Am J Gastroenterol* 1997; 92: 1887–1890.
50 Gudgeon M, Heath DI, Hurley P, et al. Trypsinogen activation peptide assay in the early severity prediction of acute pancreatitis. *Lancet* 1990; 335: 4–8.
51 Tenner S, Fernandez-del-Castillo C, Warshaw A, et al. Urinary trypsinogen activation peptide (TAP) predicts severity in patients with acute pancreatitis. *Int J Pancreatol* 1997; 21: 105–110.
52 Beechey Newman N, Rae D, Sumar N, Hermon Taylor J. Stratification of severity in acute pancreatitis by assay of trypsinogen and 1-prophospholipase A_2 activation peptides. *Digestion* 1995; 56: 271.
53 Appelros S, Thim L, Borgstrom A. Activation peptide of carboxypeptidase B in serum and urine in acute pancreatitis. *Gut* 1998; 42: 97–102.
54 Toh SKC, Johnson CD, Appelros S, Petersen U, Borgstrom A. Carboxypeptidase activation peptide and IR anionic trypsinogen as markers of severity in acute pancreatitis. *Digestion* 1997; 58 (Suppl 2): 34.
55 Gross H, Leser HG, Anderson RM, et al. Interleukin-8 and neutrophil activation in acute pancreatitis. *Eur J Clin Invest* 1992; 22: 200–203.
56 Pezzilli R, Billi P, Miniero R, et al. Serum interleukin 6, interleukin 8 and $\alpha 2$ microglobulin in early assessment of severity of acute pancreatitis. Comparison with C reactive protein. *Dig Dis Sci* 1995; 40: 2341–2348.
57 Leser HG, Gross H, Scheibenbogen C, et al. Elevation of interleukin 6 concentration precedes acute phase response and reflects severity in acute pancreatitis. *Gastroenterology* 1991; 101: 782–785.
58 Viedma JA, Perez-Mateo M, Dominguez JE, Carballo F. Role of interleukin 6 in acute pancreatitis. *Gut* 1992; 33: 1264–1267.
59 Heath DI, Cruikshank A, Gudgeon M, Jehanli A, Shenkin A, Imrie CW. Role of interleukin 6 in mediating the acute phase protein response and potential as an early means of severity assessment in acute pancreatitis. *Gut* 1993; 34: 41–45.
60 Rau B, Steinbach G, Mayer J, Gansauge F, Grünert A, Beger HG. The role of interleukin-8 in the severity assessment of septic complications in necrotising pancreatitis. *Digestion* 1997; 58 (Suppl 2): 11.
61 Pezzilli R, Billi P, Miniero R, Barakat B. Serum interleukin-10 in human acute pancreatitis. *Dig Dis Sci* 1997; 42: 1469–1472.
62 Exley AR, Leese T, Holliday MP, Swann RA, Cohen J. Endotoxaemia and serum tumour necrosis factor as prognostic markers in severe pancreatitis. *Gut* 1992; 33: 1126–1128.
63 Messmann H, Grune S. TNF and TNF receptors P55 and P75 in mild and severe acute pancreatitis. *Gastroenterology* 1997; 112: A464.
64 Paajainen H, Laato M, Jaakkola M, Pulkki A, Niinikoski J, Nordback I. Serum tumour necrosis factor compared with C-reactive protein in the assessment of severity of acute pancreatitis. *Br J Surg* 1995; 82: 271–273.
65 de Beaux AC, Goldie AS, Ross JA, Carter DC, Fearon KHC. Serum concentration of inflammatory mediators related to organ failure with acute pancreatitis. *Br J Surg* 1996; 83: 349–353.
66 Gross V, Schölmerich J, Leser HG, et al. Granulocyte elastase in assessment of severity of acute pancreatitis. Comparison with acute phase protein C reactive protein, $\alpha 1$-antitrypsin and protease inhibitor $\alpha 2$-macroglobulin. *Dig Dis Sci* 1990; 35: 97–105.
67 Uhl U, Büchler M, Malfertheiner P, Martini M, Beger HG. PMN elastase in comparison with CRP, antiproteases and LDH as indicators of necrosis in human acute pancreatitis. *Pancreas* 1991; 6: 253–259.
68 Dominguez-Muñoz JE, Carballo F, Garcia MJ. Clinical usefulness of polymorphonuclear elastase in predicting the severity of acute pancreatitis: results of a multicentre study. *Br J Surg* 1991; 78: 1230–1234.
69 Glazer G, Mann D. UK guidelines for the management of acute pancreatitis. *Gut* 1998; 42 (Suppl 2).
70 Bassi C, Falconi M, Caldiron E, Salvia R, Bertazzoni Minelli E, Pederzoli P. Use of antibiotics in necrotizing pancreatitis. *Problems Gen Surg* 1997; 13: 80–85.
71 Pederzoli P, Bassi C, Vesentini S, Campedelli A. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with Imipenem. *Surg Gynecol Obstet* 1993; 176: 480–483.

72 Saino V, Kemppainem E, Piolakkainen P, et al. Early antibiotic treatment in acute necrotizing pancreatitis. *Lancet* 1995; 346: 663–667.

73 Takeda K, Matsuno S, Sunamura M, Kakugawa Y. Cotinuous regional arterial infusion of protease inhibitor and antibiotics in acute necrotizing pancreatitis. *Am J Surg* 1996; 171: 394–398.

74 Delcenserie R, Yzet T, Ducroix JP. Prophylactic antibiotic in treatment of severe acute alcoholic pancreatitis. *Pancreas* 1996; 13: 198–201.

75 Luiten EJT, Hop WCJ, Lange JF, Bruining HA. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. *Ann Surg* 1995; 222: 57–65.

76 Schwarz M, Isenmann R, Meyer H, Beger HG. Antibiotic use in necrotizing pancreatitis. Results of a controlled study. *Deutsche Medizinsche Wochenschrift* 1997; 122: 356–361.

77 Bassi C. Infected pancreatic necrosis. *Int J Pancreatol* 1994; 16: 1–10.

78 Johnson CD. Antibiotic prophylaxis in severe acute pancreatitis. *Br J Surg* 1996; 83: 883,884.

79 Powell JJ, Miles R, Siriwardena A. Antibiotic prophylaxis in the initial management of severe acute pancreatitis. *Br J Surg* 1998; 85:582–587.

80 Carr-Locke DL. Role of endoscopy in gallstone pancreatitis. *Am J Surg* 1993; 163: 519–521.

81 Fan ST, La SC, Mok FPT, Lo CH, Rheng SS, Wong J. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. *N Engl J Med* 1993; 328: 228–232.

82 Neoptolemos JP, London NJ, James D, Carr-Locke DL, Bailey IA, Fossard DP. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conventional treatment for acute pancreatitis due to gallstones. *Lancet* 1988; 11: 979–983.

83 Nowak A, Nowakowsca-Dulawa E, Marek TA, Rybicka J. Final results of the prospective, randomized, controlled study on endoscopic sphinterotomy versus conventional management in acute biliary pancreatitis. *Gastrenterology* 1995; 108: (A380).

84 Folsch UR, Nitsche R, Ludtke R, Hilgers RA, Creutzfeldt W, the German Group on Acute Pancreatitis. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. *N Engl J Med* 1997; 336: 237–242.

85 Koretz R. Nutritional support in pancreatitis: feeding an organ that has eaten itself. *Ann Gastrointest Dis* 1993; 4: 99–115.

86 Kalfarentzos F, Kehagias J, Mead N, Kokkinis K, Gogos CA. Enteral feeding is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized propsective trial. *Br J Surg* 1997; 84: 1665–1669.

87 Windsor AJC, Kanwar S, Li AJK, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut* 1998; 42: 431–435.

88 Kingsnorth AN, Galloway SW, Formela LJ. Randomised double-blind phase II trial of lexipafant, a platelet-actvating factor antagonist, in human acute pancreatitis. *Br J Surg* 1995; 82: 1414–1420.

89 McKay CJ, Curran F, Sharples C, Baxter JN, Imrie CW. Prospective placebo-controlled randomized trial of lexipafant in predicted severe acute pancreatitis. *Br J Surg* 1997; 84: 1239–1243.

90 Toh SKC (for the British Acute Pancreatitis Study Group). Lexipaphant, a platelet activation factor antagonist reduces mortality in a randomised placebo-controlled study in patients with severe acute pancreatitis *Gut* 1997; 40 (Suppl 1): A12.

91 Buchler M, Malfertheiner P, Uhl W, Scholmerich J, Stockmann F, Adler G, et al. Gabexate mesilate in human acute pancreatitis. *Gastroenterology* 1993; 104: 1165–1170.

92 Pederzoli P, Cavallini G, Falconi M, Bassi C. Gabexate mesilate vs aprotinin in human acute pancreatitis (GA.ME.P.A.): A prospective randomized double-blind multicenter study. *Int J Pancreatol* 1993; 14: 117–124.

93 Messori A, Rampazzo R, Scroccaro G, Olivato R, Bassi C, Falconi M, et al. Effectiveness of gabexate mesilate in acute pancreatitis, a metaanalysis. *Dig Dis Sci* 1995; 40: 734–738.

94 Carballo F, Domingues E, Fernandes-Calvet L, et al. Is somatostatin useful in the treatment of acute pancreatitis? A metaanalysis. *Digestion* 1994; 55: 16–19.

95 McKay CJ, Baxter JN, Imrie CW. A randomized, controlled trial of octreotide in moderate to severe acute pancreatitis. *Int J Pancreatol* 1997; 21: 13–21.

96 Uhl W, Malfertheiner P, Adler G, et al. The role of octreotide in human acute pancreatitis. A multicenter study. *Digestion* 1997; 58: 9 (A32).

97 Cavallini G, Tittobello A, Frulloni L, Masci E, Mariani A, Di Francesco V, et al. Gabexate for the prevention of pancreatic damage related to endoscopic cholangiopancreatography. *N Engl J Med* 1996; 335: 919–923.

98 Poston GJ, Wiliamson CN. Surgical managment of acute pancreatitis. *Br J Surg* 1990; 77; 5–12.

99 D' Egidio A, Schein M. Surgical strategies in the treatment of pancreatitc necrosis and infection. *Br J Surg* 1991; 78: 133–137.

100 Farthmann EH, Lausen M, Schoffel U. Indications for surgical treatment of acute pancreatitis. *Hepatogastroenterology* 1993; 40: 556–562.

101 Uomo G, Visconti M, Manes G, et al. Nonsurgical treatment of acute necrotizing pancreatitis. *Pancreas* 1996; 12; 142–148.

102 Bradley EL, Allen K. A prospective longitudinal study of observation versus surgical intervention in the managment of necrotizing pancreatitis. *Am J Surg* 1991; 161: 19–24.

103 de Beaux AC, Palmer KR, Carter DC. Factors influecing morbidity and mortality in acute pancreatitis; an analysis of 279 cases. *Gut* 1995; 37: 121–126.

104 Beger HG, Buchler M, Bittner R, Block S, Nevalainen T, Roscher R. Necrosectomy and postoperative local lavage in necrotizing pancreatitis. *Br J Surg* 1988; 75: 207–212.

105 Renner IG, Savage WT III, Pantoja JL. Death due to acute pancreatitis: a retrospective analysis of 405 autopsy cases. *Dig Dis Sci* 1985; 30: 1005–1018.

106 Karimagni I, Kathaleen A, Porter A, Langevin RE, Banks PA. Prognostic factors in sterile pancreatic necrosis. *Gastroenterology* 1992; 103: 1636–1640.

107 Foitzik T, Klar E, Buhr HJ, Herfarth C. Improved survival in acute necrotizing pancreatitis despite limiting the indications for surgical debridement. *Eur J Surg* 1995; 161: 187–192.
108 Pederzoli P, Cavallini G, Bassi C, Falconi M. Sterile necrosis: surgical indications? in *Facing Pancreatic Dilemma*, Pederzolli P, Bassi C, Cavallini G (eds.), Springer-Verlag, Heidelberg, 1994, pp. 43–65.
109 Fernandez-Cruz L, Navarro S, Valderama R, et al. Acute necrotizing pancreatitis: a multicentre study. *Hepatogastroenterology* 1994; 41: 185–189.
110 Gerzof SG, Banks PA, Robbins AH, et al. Early diagnosis of pancreatic infection by computed tomography-guided aspiration. *Gastroenterology* 1987; 93: 1315–1320.
111 Banks PA, Gerzof SG, Langevin RE, Silverman SG, Sica GT, Hughes MD. CT-guided aspiration of suspected pancreatic infection: bacteriology and clinical outcome. *Int J Pancreatol* 1995; 18: 265–270.
112 Rau B, Pralle U, Mayer JM, Beger HG. The role of fine-needle aspiration in the diagnosis of infected pancreatic necrosis: an 8 year experience. *Br J Surg* 1998; 85: 179–184.
113 Bradley EL. A fifteen year experience with open drainage for infected pancreatic necrosis. *Surg Gynecol Obstet* 1993; 177: 215–222.
114 Wilson C, McArdle CS, Carter DC, Imrie CW. Surgical treatment of acute necrotizing pancreatitis. *Br J Surg* 1988; 75: 1119–1123.
115 Farkas G, Marton J, Mandi Y, Szederkenyi E. Surgical strategy and managment of infected pancreatic necrosis. *Br J Surg* 1996; 83: 930–933.
116 Teerenhovi O, Nordback I, Eskola J. High volume lesser sac lavage in acute necrotizing pancreatitis. *Br J Surg* 1989; 76: 370–373.
117 Johnson CD. Timing of intervention in acute pancreatitis. Postgrad Med J 1993; 69: 509–515.