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Current management of acute pancreatitis

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SUMMARY

The incidence of acute pancreatitis varies considerably between regions and is estimated at 5–80 per 100,000 population. The mortality rate of acute edematous-interstitial pancreatitis is below 1%, whereas 10–24% of patients with severe acute pancreatitis die. The early prognostic factors that can be used to determine whether the clinical course is likely to be severe are three or more signs of organ failure according to the Ranson or Imrie scores, the presence of nonpancreatic complications, and the detection of pancreatic necrosis by imaging techniques. Elevated C-reactive protein levels above 130 mg/l can also predict a severe course of acute pancreatitis with high sensitivity. Although no causal treatment exists, replacing the dramatic fluid loss that takes place in the early disease phase is critical and determines the patient's prognosis. Adequate pain relief with opiates is another therapeutic priority. In patients with pancreatic necrosis, the high mortality rate between the third and fourth week after the initial episode is determined largely by the development of pancreatic infection, and can therefore be reduced by early antibiotic treatment. Early enteral nutrition for the treatment of acute pancreatitis has been shown to be superior and much more cost-effective than parenteral nutrition. Infected pancreatic necrosis or pancreatic abscess are two of the few remaining indications for open surgery in acute pancreatitis. Even when indicated, surgery is frequently delayed or even replaced by minimally invasive surgical techniques.

KEYWORDS antibiotic treatment, enteral nutrition, interventional treatment, prognostic factors, surgical treatment

REVIEW CRITERIA

This review is based on a search of PubMed with the MeSH terms: "treatment of acute pancreatitis", "antibiotics in acute pancreatitis", "prognostic markers in acute pancreatitis", "diagnostic procedures in acute pancreatitis", "pain management in acute pancreatitis", "role of endoscopy in acute pancreatitis", and "surgical and interventional necrosectomy in acute pancreatitis", either alone or in combination. The search was performed in May 2005 for papers published after 2000. Papers from the authors' own collection were also included. Only full papers were included in this review.

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INTRODUCTION

Acute pancreatitis is one of the most common gastroenterological diseases. The incidence of acute pancreatitis per 100,000 population ranges from 5–80 cases per year, with the highest incidence rates seen in Finland and the US.[1] Of all patients admitted to hospital, 2% are diagnosed with acute pancreatitis. Clinical symptoms (belt-like abdominal pain and vomiting) together with elevated plasma concentrations of pancreatic enzymes are the cornerstone of diagnosis.

Mild edematous disease occurs in 75–85% of acute pancreatitis cases and has a mortality rate of below 1%, whereas severe acute pancreatitis occurs in 15–25% of cases and has a mortality rate of 10–24%. Both clinical varieties, mild and severe, can occur regardless of the underlying etiology of the disease. In 80% of cases, acute pancreatitis is caused by either gallstone disease or excessive alcohol consumption; pancreatitis caused by hypercalcemia, hyperlipidemia, infectious agents or following endoscopic retrograde cholangiopancreaticography (ERCP) or cardiac surgery is much less common.

During the past 20 years, a considerable reduction in mortality associated with acute pancreatitis has been recorded.[2] Adequate medical treatment invariably involves hospital admission, as the need for intensive care treatment can arise quickly or unexpectedly. The requirement for frequent clinical assessments, repeated laboratory studies and the use of advanced imaging techniques, such as CT or MRI, strongly argues against treating acute pancreatitis on an outpatient basis.

DIAGNOSTIC AND PROGNOSTIC MARKERS OF ACUTE PANCREATITIS

A prediction of the course and outcome of acute pancreatitis is needed most when the patient first presents in the emergency room, but it is often rather difficult to make such a prediction. For example, although enzymatic activity of serum amylase and lipase is used to diagnose pancreatitis, it is not helpful in determining disease severity.

Box 1 Grading the severity of acute pancreatitis using CT.

Balthazar and co-workers first developed a CT severity index to determine the morphologic severity of acute pancreatitis.[5] Silverman, Banks and colleagues later simplified and extended the index to monitor organ failure.[6] The modified CT-grading system is shown here.

Evaluation of pancreatic morphology, without taking into account the extent of pancreatic necrosis	
0 points, Grade A	Normal pancreas consistent with mild pancreatitis
2 points, Grade B/C	Focal or diffuse enlargement of the gland including contour irregularities and inhomogeneous attenuation with or without peripancreatic inflammation
4 points, Grade D/E	Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis
Additional 2 points	Extra-pancreatic complications (one or more of the following: pleural effusion, ascites, vascular complications, parenchymal complications, or gastrointestinal tract involvement)
Scoring for pancreatic necrosis	
0 points	No pancreatic necrosis
2 points	≤30% pancreatic necrosis
4 points	>30% pancreatic necrosis

GLOSSARY

RANSON SCORE
A score that uses age, leukocyte count, serum glucose level, serum lactate dehydrogenase and serum glutamate-oxalacetate transaminase at admission and 48 h after admission to predict a severe course of acute pancreatitis

IMRIE SCORE
A score that uses age, leukocyte count, glucose level, serum lactate dehydrogenase, serum calcium, urea, and arterial pO_2 only 48 h after admission to predict the severity of acute pancreatitis (sensitivity = 80%; specificity = 87%)

DYNAMIC CONTRAST-ENHANCED CT (DCT)
Cross-sectional imaging of the brain or internal organs to detect abnormalities that might not show on an ordinary X-ray; assisted by the injection of iodine-containing contrast media

Although in 75–80% of cases acute pancreatitis is a mild disease without associated mortality, it is important to identify the 20–25% of patients who are likely to develop severe disease associated with major complications and who would benefit from early intensive-care monitoring and treatment. In addition to an initial clinical assessment by an experienced gastroenterologist or surgeon, there are several prognostic markers and scoring systems that help to distinguish severe from mild disease. If a patient presents with three or more laboratory signs of organ failure (such as a fall in pO_2 or a rise in creatinine levels) according to the RANSON SCORE or the IMRIE SCORE, if an overt extra-pancreatic complication develops (e.g. respiratory or renal insufficiency), or if pancreatic necrosis is diagnosed by a contrast-enhanced CT scan, then the course of the disease is more likely to be severe.[3,4]

CT and MRI

DYNAMIC CONTRAST-ENHANCED CT (DCT) is the imaging modality of choice for staging acute pancreatitis and for detecting complications.[5] DCT has been shown to detect pancreatic parenchymal necrosis with a diagnostic sensitivity of 87% and an overall detection rate of 90%.[5,6] DCT therefore has two major roles in the evaluation of patients with known or suspected acute pancreatitis: first, it is used for the initial staging of the severity of the inflammatory process; and second, it is used for the early detection of pancreatic and extra-pancreatic complications. Although the application of contrast media has been found to aggravate acute pancreatitis in certain animal models, an extensive analysis by Uhl and co-workers showed that absolutely no negative effect of contrast-enhanced CT is to be expected in humans, and that the benefits of a CT diagnosis far outweigh its risks in pancreatitis patients.[7] On the other hand, a CT scan of the pancreas without intravenous contrast enhancement is worthless for investigating pancreatitis.

The morphologic severity of acute pancreatitis can be determined using a CT severity index (CTSI) that was developed by Balthazar and co-workers and then simplified and extended to monitor organ failure by Silverman, Banks and colleagues in 2004 (Box 1, Figure 1).[5,6] Comparison of the original CTSI with mortality showed a good correlation between higher CTSI values and mortality and morbidity (Table 1), and this holds true for the modified CTSI. Furthermore, the modified CTSI correlates well with the length of hospital stay and the development of organ failure.[3,5,6]

While contrast-enhanced, multislice CT remains the gold standard for imaging acute pancreatitis (Figure 1), the usefulness of MRI in this setting has been investigated in several studies. MRI not only avoids the administration of radiation and nephrotoxic contrast media, but is also highly suited to the detection of vascular complications, such as pseudoaneurysms and venous thromboses. A recent study reported that, compared with the Ranson score as a gold standard, MRI detected severe acute pancreatitis with 83% sensitivity (58–96%, 95% CI) and 91% specificity (68–98%), whereas the sensitivity for CT was 78% (52–93%) and its specificity 86% (63–96%).[8]

Unfortunately, MRI is not universally available, is unsuitable for patients with ferromagnetic implants, and is rather expensive. For this reason, current guidelines recommend DCT as the imaging procedure of choice, regarding DCT as mandatory for patients with persistent organ failure, for those who develop systemic inflammatory response syndrome or sepsis, for those who fail to improve within 6–10 days into the disease course, and for those with probable

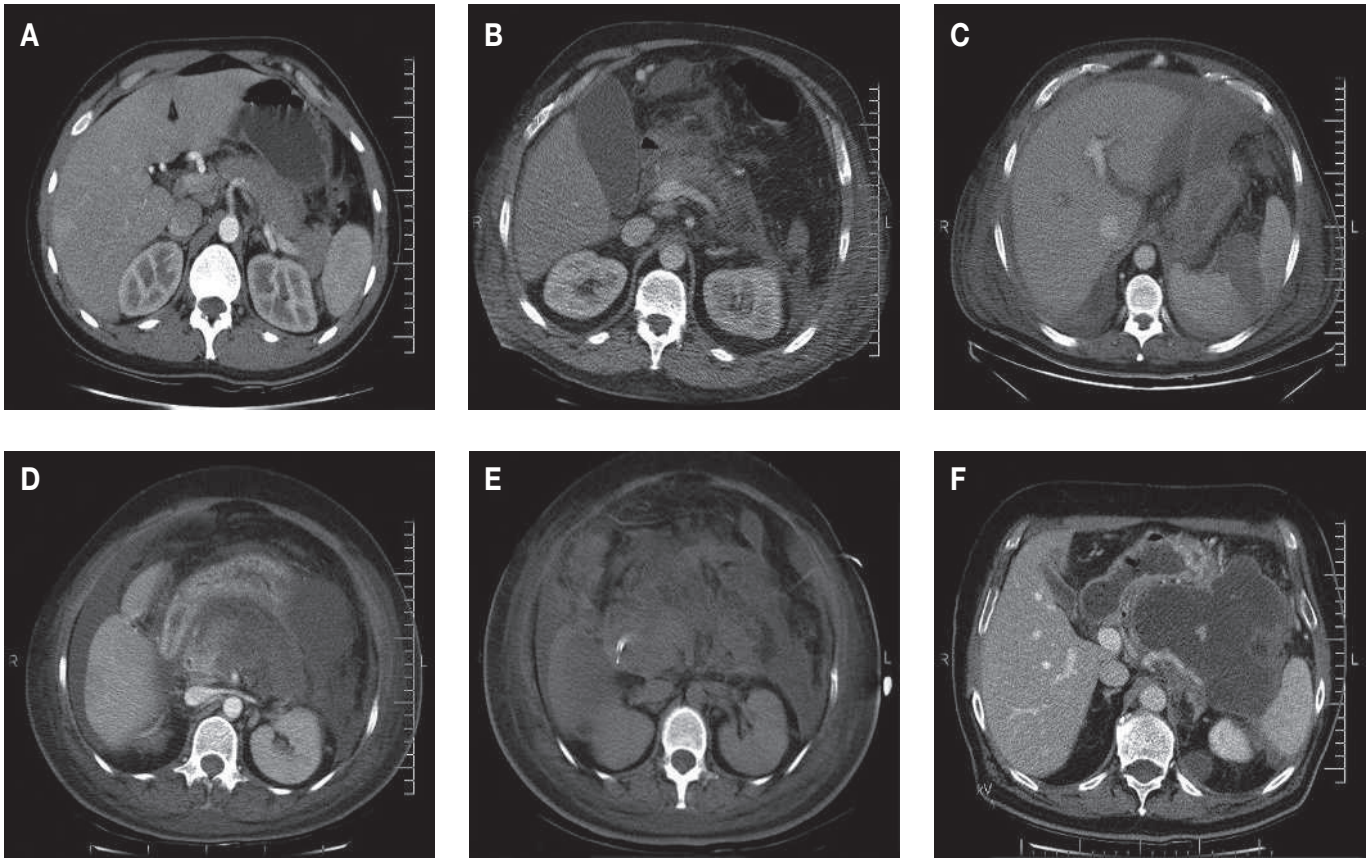

Figure 1 Axial contrast-enhanced CT scans of acute pancreatitis. (**A**) A pancreas with mild pancreatitis and no signs of pancreatic necrosis (CTSI: Grade A, 0 points). (**B**) Diffuse enlargement of the gland, including contour irregularities and inhomogeneous attenuation with peripancreatic inflammation consistent with edematous post-ERCP pancreatitis 24 h after ERCP (CTSI: Grade B, 2 points). (**C**) The patient in (B) 20 days after ERCP. The scan shows pancreatic and peripancreatic fluid collection as well as peripancreatic fat necrosis, extra-pancreatic complications, such as pleural effusion and ascites, and vascular complications, such as the embolic obstruction of the superior mesenteric artery resulting in infarction of the spleen (CTSI: Grade E, 4 points plus 2 additional points for extra-pancreatic complication plus 4 points for >30% pancreatic necrosis). (**D**) Pancreatic and peripancreatic fluid collection as well as peripancreatic fat necrosis (CTSI: Grade D, 4 points plus 4 points for pancreatic necrosis [more than 30% necrotic pancreatic parenchyma]). (**E**) Scan suggesting peripancreatic and complete pancreatic necrosis. Placement of a percutaneous drain into the pancreatic fluid collection (CTSI: Grade E, 6 points plus 4 additional points for pancreatic necrosis). (**F**) Organized pancreatic fluid collection and a developing pseudocystic wall, complete obstruction of the duodenum and no signs of superinfection 8 weeks after biliary necrotizing pancreatitis (Balthazar score or modified CTSI are not applicable). CTSI, CT severity index (here, the modified CTSI of Silverman and Banks and colleagues); ERCP, endoscopic retrograde cholangipancreatography.

infected pancreatic necrosis (evidence-based medicine [EBM] recommendation grade B).[9]

C-reactive protein

As a stand-alone prognostic marker, an elevated C-reactive protein (CRP) concentration of greater than 130 mg/l indicates that acute pancreatitis has a complicated course with a sensitivity of 85% in the first 72 h after the onset of symptoms. Although detection of elevated CRP levels is sensitive for severe acute pancreatitis it is not specific for the disease, and other causes of inflammation such as cholangitis and pneumonia need to be ruled out before severity assessment by measurement of CRP.[10]

Trypsinogen and trypsinogen activation peptide

In an attempt to use the extent of pancreatic zymogen activation to determine the severity of acute pancreatitis, trypsinogen activation peptide (TAP) levels have been evaluated.[11] Urinary TAP concentrations have been shown to correlate well with the severity of acute pancreatitis at admission, but its measurement by a manual enzyme immunoassay combined with the limited

GLOSSARY

ALTERNATIVE SPLICING
Various ways of splicing out introns in eukaryotic pre-messenger RNAs, which results in one gene producing several different mRNAs and protein products

Table 1 Predicting morbidity and mortality rates in patients with acute pancreatitis using CT, combining scores for pancreatic morphology and extent of pancreatic necrosis.[a]

Index	Predicted morbidity rate	Predicted mortality rate
0–3	8%	3%
4–6	35%	6%
7–10	92%	17%

[a]Based on the original CT severity index of Balthazar and co-workers.[5]

stability of the TAP assay restricts its use as an emergency-room test. Employing a similar principle, a Finnish group developed a dipstick test for urinary trypsinogen-2.[12] This group was able to show a higher positive-likelihood ratio for the urinary trypsinogen-2 test strip than for CRP 24 h after admission. To evaluate this method further, multicenter trials need to be conducted.

Hematocrit

An exciting development is the use of hematocrit as a prognostic marker for the severity of acute pancreatitis. This development emphasizes the pathophysiological role of fluid loss in determining the severity of pancreatitis and the role of vigorous fluid replacement in the prognosis of the disease. A hematocrit of more than 44% on admission, or the absence of a fall in hematocrit during the first 24 h after admission, indicates pancreatic necrosis with a positive predictive value of 96%, and multiorgan failure with a positive predictive value of 97%.[13] A retrospective data analysis from Germany could not entirely reproduce these data, but confirmed that a normal hematocrit predicted the absence of pancreatic necrosis with a high negative predictive value.[14]

Procalcitonin

Another marker that has been evaluated as a prognostic indicator for pancreatitis is procalcitonin, which is encoded by the *CALCA* gene. Proinflammatory cytokines, as well as bacterial lipopolysaccharides, strongly induce the synthesis and release of procalcitonin in inflammation. Although there have been numerous attempts to unravel the biological function of procalcitonin, its physiological role in inflammation and sepsis is far from being understood. Nevertheless, a remarkable number of clinical studies have demonstrated the pivotal role of this parameter in the host response to microbial and fungal infections and have shown a strong correlation between this marker and disease severity. In addition, high serum levels of procalcitonin implicate the synthesis of the calcitonin-gene-related peptide by ALTERNATIVE SPLICING of the *CALCA* RNA, which directly induces peripheral vasodilatation and the extravasation of fluid. As a consequence, hypovolemia, which is causally related to multiorgan failure, can occur.

It remains controversial whether high procalcitonin levels should be regarded as a valuable marker for the prediction of either infected necrosis in acute pancreatitis or a severe course of this disease. A meta-analysis published earlier this year indicated that procalcitonin cannot be regarded as a good marker for assessing the severity of pancreatitis;[15] however, an unpublished multicenter European trial has announced somewhat more promising data.[16]

TREATMENT OF ACUTE PANCREATITIS

Fluid resuscitation and rehydration

Maintaining an adequate intravascular volume is probably the most essential therapeutic measure in the treatment of acute pancreatitis—if not achieved, it is also the most consequential mistake. Patients with acute pancreatitis can sequester large amounts of fluid not only into the retroperitoneal space and the intraperitoneal cavity (pancreatic ascites), but also into the gut and the pleural space. Adequate fluid resuscitation might initially require more than 10 l of either crystalline or colloidal fluids to be given within 24 h of admission.

Experimentally, hemodilution to a hematocrit of around 30% with dextran 60 improves pancreatic microcirculation and oxygenation.[17] Currently there are no data available as to whether colloid or crystalline solutions are superior for fluid replacement in humans and whether colloids improve pancreatic microcirculation and disease outcome. The authors' clinical practice would suggest that a ratio of 1:3 for colloids and crystals is preferable.

To determine the required fluid volume to be resuscitated, the central venous pressure should be closely monitored and hourly urine excretion rates and daily hematocrit measurements taken. Central venous pressure should be raised to between 8 and 12 cm H_2O. Alternatively, intravascular blood volume can be monitored by thermodilution (e.g. using the PiCCO® system; Pulsion Medical Systems, Munich, Germany) and adjusted to the manufacturer's reference values. Fluids are given intravenously until the urine output can be maintained at above 0.5 ml/kg bodyweight per hour. Adequate fluid substitution can also be assumed when the hematocrit falls to between 30 and 35%. Besides fluid resuscitation, there is also increasing evidence that oxygen supplementation to maintain an arterial saturation of 95% is associated with the resolution of organ failure.[18]

Enteral nutrition versus total parenteral nutrition

Patients with severe acute pancreatitis are frequently hypercatabolic, and a timely initiation of feeding is important if malnutrition is to be avoided or treated. Nevertheless, in the past, patients with acute pancreatitis received nil by mouth as it was believed that any stimulation of the exocrine pancreas by fluid or solid nutrients would negatively affect the disease course. Today, we know that the pancreas is pretty much 'at rest' during pancreatitis and that restoring secretion would be a much more physiological strategy than resting the organ.

Increasing evidence suggests that enteral feeding is not only safe but can also reduce complications by helping to maintain the intestinal barrier function and intestinal blood flow, and by preventing or reducing bacterial translocation from the gut. Furthermore, enteral nutrition eliminates some of the complications of parenteral nutrition, such as catheter sepsis, which occurs in 2% of patients even if the catheter is managed appropriately, as well as other less common complications.

From a number of prospective randomized clinical trials,[19–25] evidence has emerged that enteral nutrition is superior to parenteral nutrition in outcome. When we subjected the available data to a meta-analysis, it became clear that the rates of organ failure and pancreatic infection, as well as the length of hospital stay, were significantly improved when enteral nutrition, rather than parenteral nutrition, was administered to acute pancreatitis patients (Figure 2). The most dramatic outcome measure in favor of enteral nutrition was, of course, cost, which amounts to only 20% of that of parenteral nutrition. Not only were these outcomes confirmed by another meta-analysis,[26] but no trials have shown a benefit for parenteral nutrition—a fact not to be ignored by those still hesitant about using enteral nutrition for patients with acute pancreatitis.

In some cases it is impossible for enteral nutrition alone to meet the caloric intake required to prevent catabolism. In such cases, some enteral nutrition should still be given via a nasogastric or nasojejunal feeding tube to prevent atrophy of the intestinal mucosa and loss of barrier function. There is also evidence that an enrichment of intravenous nutrition with glutamine could reduce leaky bowel syndrome, but experience in patients with pancreatitis is still limited.[27]

To overcome the delayed gastric emptying associated with acute pancreatitits or paralytic ileus, the placement of a nasogastric or nasointestinal tube is still indicated. By contrast, continuous suction of gastric juice to prevent stimulation of the pancreas is obsolete for the above-mentioned reasons.[28] As most patients find nasogastric suction very uncomfortable, only those with ileus should be treated in this manner.

To investigate the route of enteral nutrition, a group from Glasgow recently compared enteral nutrition via a nasojejunal tube with enteral nutrition via a nasogastric tube in a randomized controlled trial involving 50 consecutive patients.[29] No disadvantages were found for nutrition via nasogastric tube. When taking into account the frequent rate of dislocations of nasojejunal tubes and their required endoscopic replacements, nasogastric enteral feeding might well emerge as the more feasible option for the nutrition of acute pancreatitis patients in clinical practice.

The decision when and with what kind of diet to begin oral feeding arises for most patients during their recovery from acute pancreatitis. Oral feeding can cause a relapse of pain and disease recurrence—the risk of pain relapse is 21% whenever oral feeding is started. Half of the episodes of pain relapse occur on the first or second day of oral refeeding, with a greater risk if the patient recovers from severe or necrotizing pancreatitis. It is recommended that oral feeding should be started with a food that is readily

GLOSSARY

APACHE II SCORE
Acute Physiology And Chronic Health Evaluation score; a scoring system used to quantify the severity of disease of intensive care patients, based on physiologic and laboratory measurements, age and previous health status

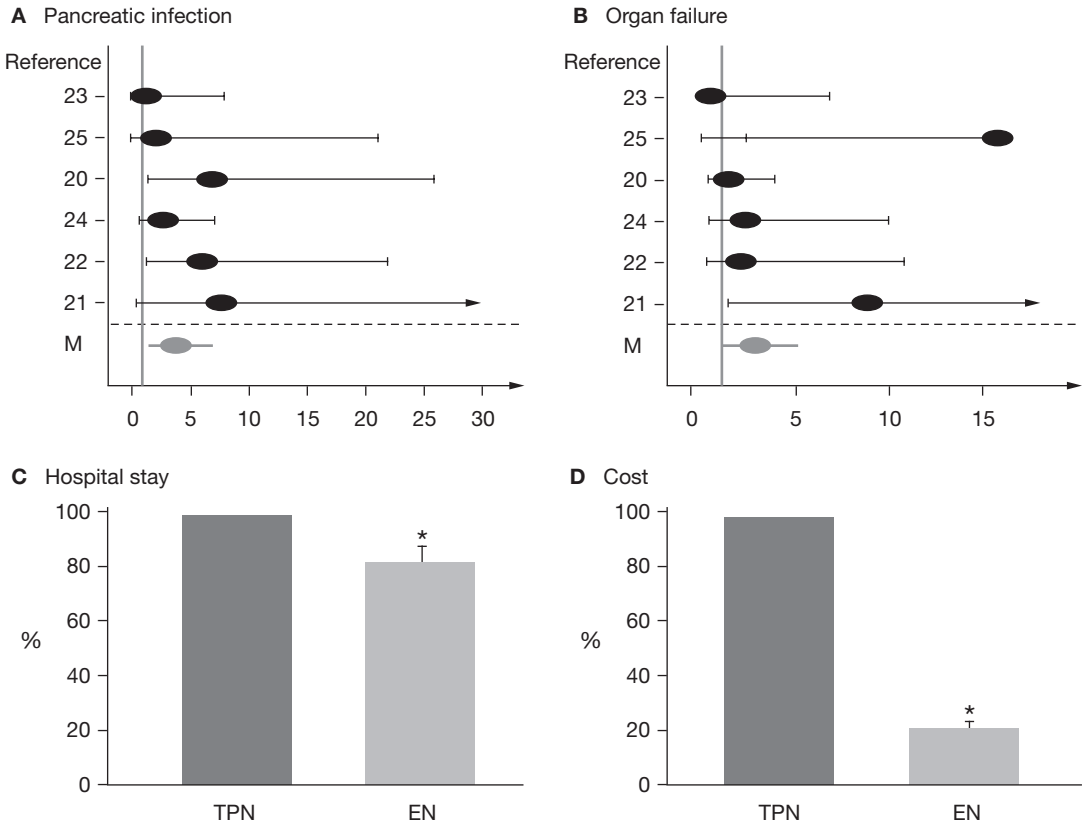

Figure 2 Meta-analysis of studies comparing enteral nutrition with parenteral nutrition in severe acute pancreatitis. Data analysis from studies described in references 20–25. In the TPN group 138 (85 males and 53 females) were included, while in the EN group 125 patients (73 males and 54 females) were eligible for analysis. The mean age was 54.35 ± 8.13 years in the TPN group and 55.63 ± 7.47 years in the EN group. The APACHE II SCORE was calculated as 13.425 ± 4.7 for the TPN group and 11.55 ± 3.5 for the EN group. Analysis showed a reduction in infected necrosis in patients receiving enteral nutrition (**A**) as well as a reduction in organ failure when patients were fed enterally (**B**). Patients with enteral nutrition were discharged significantly earlier from hospital (P <0.02) (**C**). The cost of enteral nutrition was only 20% of that of parenteral nutrition (P <0.01) (**D**). In conclusion, enteral nutrition has a clear benefit over total parenteral nutrition regarding the course of necrotizing pancreatitis. In the Forest plots shown in (**A**) and (**B**) the dashed lines indicate an effect size of 1.0 (no effect). The gray bar indicates the calculated effect size of all studies included in the analysis comparing enteral versus parenteral nutrition. An effect size >1.0 indicates a positive effect for enteral nutrition, whereas an effect size <1.0 indicates a positive effect for parenteral nutrition. Asterisks in (**C**) and (**D**) indicate statistically significant differences at the 5% level. The odds ratio was calculated as 3.5 in the meta-analysis for pancreatic infection (**A**) and as 2.4 for organ failure outcome (**B**). EN, enteral nutrition; M, meta-analysis; TPN, parenteral nutrition.

digestible and whenever the patient is free of pain. The value of taste-free and nutrition-free 'pancreas diets' is rather questionable and is not supported by clinical studies.[30]

Treatment of pain

Activation of pancreatic proteases and tissue necrosis causes inflammatory mediators to be released locally. These inflammatory mediators not only facilitate inflammation but can also have a direct effect on sensory nerve fibers in the celiac plexus (spinal cord level T5–T9) and therefore mediate visceral pain. Patients with acute pancreatitis often suffer from severe visceral pain. Adequate pain relief is therefore one of the most important and urgent treatment goals. In general, the combination of a non-opiate analgesic with a drug that has an effect on the central nervous system should be considered. In German-speaking countries the systemic administration of intravenous procaine hydrochloride has long been advocated as an alternative to opiates, but

has now been shown to be completely ineffective for the treatment of pain in patients with acute pancreatitis.[31,32] Concerns that morphine analogs might negatively affect the course of pancreatitis because of their inhibitory effect on the sphincter of Oddi are unwarranted[33] and have never been shown to be of any relevance to pancreatitis patients, whose pain greatly decreases with opiates.

Some centers have begun to use thoracic epidural analgesia to treat pain in acute pancreatitis patients.[34] This medication not only leads to rapid pain relief[35] but often abolishes the need for opiates. Moreover, epidural analgesia can restore impaired gut microcirculation and therefore positively affect the development of subileus or ileus (A Sielenkämper *et al.*, unpublished data).

Although quite effective, the application of epidural analgesia requires considerable technical skills and some patients do not qualify for this pain relief (e.g. those with impaired hemostasis or those on strong sedatives in whom complications of the procedure might go unnoticed).

The role of antibiotics in the treatment of acute pancreatitis

Because the development of infected pancreatic necrosis significantly increases the mortality of patients with acute pancreatitis, much attention has been given to the prevention and early treatment of gram-negative pancreatic sepsis. The major source of gram-negative bacteria is the gut, and one way of potentially preventing infected necrosis is to selectively decontaminate the intestine with non-absorbable antibiotics. In one prospective controlled clinical trial on selective intestinal decontamination, the rate of pancreatic infection was reduced in patients who received neomycine.[36] Gram-negative intestinal colonization, on the other hand, was associated with a 3.7-fold increase in mortality.[37]

As small-bowel bacterial overgrowth and subsequent bacterial translocation are regarded as responsible for most pancreatic infections, in September 2004 the Dutch Acute Pancreatitis Study Group proposed a protocol for a double-blind, placebo-controlled, randomized multicenter trial to evaluate the role of probiotic prophylaxis (*Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus salivarius*, *Lactococcus lactis*, *Bifidobacterium bifidum* and *Bifidobacterium lactis*) in patients with predicted severe acute pancreatitis.[37] Results of this trial are expected in 2006.

During the last three decades the controversial use of systemic antibiotics in the treatment of pancreatitis has been discussed, and accepted concepts have regularly been changed. The predominant bacterial strains found in pancreatic tissue or blood cultures from pancreatitis patients are *Escherichia coli*, and *Enterococcus*, *Klebsiella*, *Staphylococcus* and *Pseudomonas* spp.[38,39] Recent studies have shown that prophylactic antibiotic treatment in mild disease has no beneficial effect, and only leads to the selection of antibiotic-resistant bacterial strains.

Infected pancreatic necrosis is associated with a mortality of up to 70–80%, and patients with proven pancreatic necrosis might therefore benefit from prophylactic antibiotic treatment. A number of studies have addressed this issue and the prevailing opinion today suggests four things. First, between 25–72% of pancreatic necroses become infected. Second, infection of pancreatic necrosis most frequently develops between week 2 and week 4 from disease onset. Third, certain antibiotics such as clindamycin, imipenem, meropenem, metronidazole, and the fluoroquinolones and cephalosporins, can reach the pancreatic tissue at sufficiently high concentrations, whereas aminoglycosides do not. Fourth, early antibiotic treatment of patients with pancreatic necrosis could have a significant beneficial effect on outcome and mortality.[40–42]

A number of studies have shown the carbapenems to be effective in reducing infected pancreatic necrosis and mortality, whereas the most recent multicenter trial to have investigated the combination of ciprofloxacin and metronidazole versus placebo found no beneficial effect.[41] Whether this indicates that carbapenems are significantly more effective than chinolones plus metronidazole, or that this trial failed to include patients with severe enough pancreatitis (Ranson score between 2 and 3), remains unclear at this point.

One possible complication from the uncritical use of broad-spectrum antibiotics might be the promotion of fungal pancreatic infections. In 20% of resection specimens taken from patients with necrotizing pancreatitis, fungal infection was detected together with evidence of fungal infection in blood culture from the same patient.[43] Several of these patients suffered from fungal sepsis that was not adequately treated.

Prophylactic fluconazole treatment was shown to reduce *Candida* spp. infections in a retrospective study but failed to affect mortality.[44] Tissue penetrance into the pancreas has been assessed solely for fluconazole.[45] Whether antimycotic treatment is beneficial in necrotizing pancreatitis, whether broad-spectrum antibiotic treatment ought to be combined with antifungal agents, and which antimycotic drug besides fluconazole penetrates pancreatic necrosis or is most effective in pancreatitis, needs to be assessed in randomized trials. Although fungal growth in pancreatic necrosis is clearly associated with a worse prognosis than bacterial infection alone, none of the available studies suggest that the risk of fungal infection outweighs the benefits of broad-spectrum antibiotic treatment in necrotizing pancreatitis. The alternative is not to abandon the use of antibiotics but to combine them with antimycotic agents from the start.

Endoscopic sphincterotomy

Alcohol abuse and gallstone disease account for approximately 80% of cases of acute pancreatitis. It is still uncertain whether gallstones merely initiate or also maintain biliary acute pancreatitis. Most gallstones that cause acute pancreatitis pass spontaneously through the ampulla of Vater into the duodenum and can subsequently be recovered from the feces within a few days.

There has been much interest in the early surgical or endoscopic removal of gallstones retained in the common bile duct in patients with acute pancreatitis. Although ERCP has no role in the initial diagnosis of acute pancreatitis, there is good evidence that early endoscopic sphincterotomy with the aim of removing obstructing gallstones is the procedure of choice in patients with cholangitis or with impacted stones. Controversy remains about the timing, indication and patient selection for emergency ERCP within the first 72 h of the onset of pain.[46–48] As a rough estimate, when 26 patients with suspected biliary pancreatitis are treated with emergency ERCP and sphincterotomy, one life is expected to be saved.[49]

To discriminate between different etiologies of acute pancreatitis, laboratory tests as well as imaging techniques should be employed initially. Transabdominal ultrasound represents a basic imaging technique for acute pancreatitis in the emergency room. Its diagnostic sensitivity ranges from 28 to 80% depending on the part of the gland visualized, whereas its specificity varies between 75 and 90%. Most noteworthy and of high clinical relevance is this technique's negative predictive value of above 95% and its high sensitivity for ruling out gallbladder stones or sludge (93%).

As biliary microlithiasis is increasingly recognized as a major cause of recurrent idiopathic pancreatitis, endoscopic ultrasonography (EUS) is gaining in importance. In 52.4% of patients with repeatedly negative transabdominal ultrasound examinations, gallstones were ultimately diagnosed by EUS, and patients subsequently underwent endoscopic papillotomy and cholecystectomy.[50,51]

In conclusion, all patients presenting with acute pancreatitis, gallstones and a plasma bilirubin of greater than 5 mg/dl should, according to the recently released UK guidelines for the management of acute pancreatitis, undergo early ERCP during the first 72 h.[52] If these criteria are not fully met, even if there is clear evidence that pancreatitis is of biliary origin, ERCP might actually increase morbidity. Furthermore, all patients undergoing early ERCP for severe gallstone pancreatitis require endoscopic sphincterotomy, whether or not stones are found in the bile duct (EBM recommendation grades B and C). Patients with signs of cholangitis require endoscopic sphincterotomy or duct drainage by stenting to ensure relief of biliary obstruction (EBM recommendation grade A). All patients with biliary pancreatitis should undergo definitive management of gallstones without major delay after their recovery from acute pancreatitis (EBM recommendation grade C).[53]

Surgical or conservative management of acute necrotizing pancreatitis

Open surgical laparotomy in acute necrotizing pancreatitis is most commonly indicated for infected pancreatic necrosis. Clinical management therefore depends on the discrimination between sterile and infected pancreatic necrosis. Infected pancreatic necrosis is probable when retroperitoneal gas is present on the CT scan or when fine-needle aspiration (FNA) reveals bacterial or fungal growth.[38,39] The management of pancreatic necrosis in acute pancreatitis has shifted from early aggressive surgical therapy to a more conservative intensive-care management, but infected pancreatic necrosis remains the major risk factor for sepsis, often resulting in multiorgan failure and death.[54]

Only two decades ago surgical intervention was recommended when multiorgan dysfunction developed, but early surgical debridement within the first days of multiorgan dysfunction resulted in a mortality of up to 65% and put the benefit of surgery into question. The only randomized prospective trial comparing early (within the first 72 h) with late (12 days after the onset) pancreatic debridement in patients with severe necrotizing pancreatitis was terminated prematurely because of a mortality rate of 56% in the early-intervention group compared with 27% in the late-intervention group.[55] Nowadays it is generally believed that surgery should be postponed to the third or fourth week after the onset of acute pancreatitis and that this intervention is of benefit only for patients with infected pancreatic necrosis proven by FNA, Gram stain or microbiological culture. Nevertheless, it remains the obligation of the treating physician of a critically ill patient to rule out or confirm infected pancreatic necrosis as a septic focus at any stage of the disease by FNA.

Traditionally, surgical necrosectomy has been performed via open laparotomy. Four different access routes have been reported, and in the hands of experienced surgeons the mortality rate has decreased to 15%. The different outcomes of open packing, repeated laparotomy, closed packing and closed continuous lavage have recently been reviewed by Werner *et al.* Their results suggest that organ-preserving necrosectomy combined with the possibility of postoperative drainage (continuous postoperative lavage or closed packing) is the most promising strategy.[56]

A number of reports have recently shown that, for infected pancreatic necrosis, minimal invasive procedures, including percutaneous drainage, endoscopic drainage and minimally invasive surgery (such as retroperitoneoscopy), will assume a much greater role in future management strategies.[57] At present no prospective studies have investigated these minimally invasive interventional techniques for the management of infected pancreatic necrosis. Although clinical experience, including the authors' own, suggests that these procedures are effective and beneficial, controlled trials are needed to show whether these procedures can completely replace open surgery, or whether they temporarily drain infected necrosis only until a later more suitable interval for open surgery.

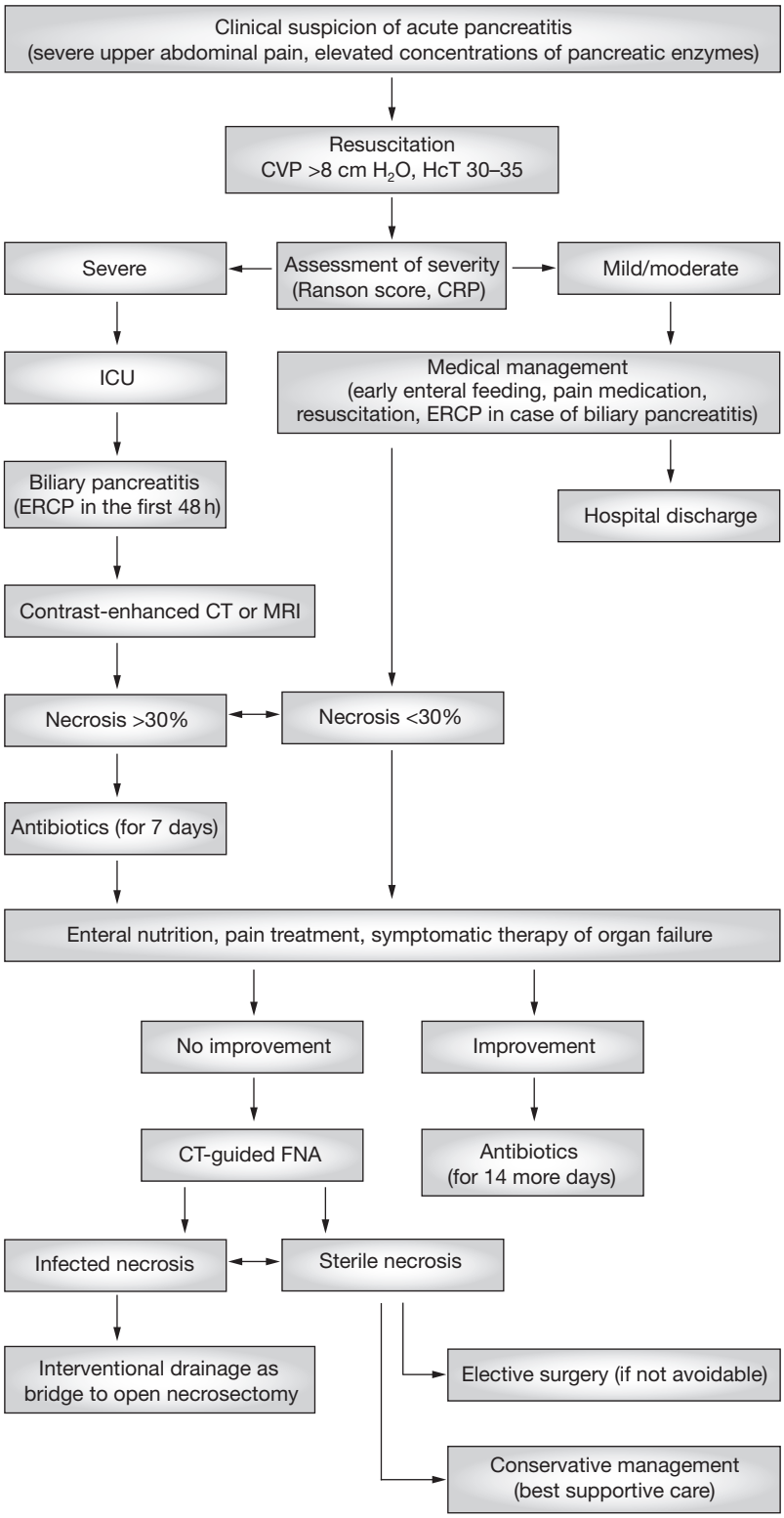

Figure 3 Algorithm for the management of acute pancreatitis at the University Hospital of Greifswald. CRP, C-reactive protein; CVP, central venous pressure; ERCP, endoscopic retrograde cholangiography; FNA, fine-needle aspiration; HcT, hematocrit; ICU, intensive care unit

CONCLUSIONS

Most attacks of acute pancreatitis are mild, with recovery occurring within a few days of the provision of simple supportive therapy as outlined above. Mild acute pancreatitits requires only adequate intravenous fluid replacement to avoid secondary organ failure, and treatment with analgesics. Converesly, patients with severe pancreatitis are at high risk of developing pancreatic necrosis, organ failure, and septic complications, resulting even nowadays in death in up to 25% of cases. The therapeutic goal in severe acute pancreatitis, as we don't have any causal treatment at hand, is to prevent the development of complications. Severe acute pancreatitis should be managed in an intensive care unit in order to apply intensive monitoring and systemic support. Furthermore, in addition to fluid resuscitation and pain treatment, three main therapeutic goals have to be achieved: the introduction of early enteral nutrition, prophylactic treatment with antibiotics and, if indicated, early endoscopic sphincterotomy in case of biliary pancreatitis (Figure 3).

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Competing interests
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