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World J Gastroenterol 2001;7(4):476-481
World Journal of Gastroenterology
 ISSN 1007-9327

• REVIEW •

Management of necrotizing pancreatitis

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Received 2001-05-15 Accepted 2001-06-15

Abstract

Infection complicating pancreatic necrosis leads to persisting sepsis, multiple organ dysfunction syndrome and accounts for about half the deaths that occur following acute pancreatitis. Severe cases due to gallstones require urgent endoscopic sphincterotomy. Patients with pancreatic necrosis should be followed with serial contrast enhanced computed tomography (CE-CT) and if infection is suspected fine needle aspiration of the necrotic area for bacteriology (FNAB) should be undertaken. Treatment of sterile necrosis should initially be non-operative. In the presence of infection necrosectomy is indicated. Although traditionally this has been by open surgery, minimally invasive procedures are a promising new alternative. There are many unresolved issues in the management of pancreatic necrosis. These include, the use of antibiotic prophylaxis, the precise indications for and frequency of repeat CE-CT and FNAB, and the role of enteral feeding.

Subject headings pancreatitis, acute necrotizing/drug therapy; pancreatitis, acute necrotizing/surgery; biopsy, needle; tomography, x-ray computered; enteral nutrition; human

Slavin J, Ghaneh P, Sutton R, Hartley M, Rowlands P, Garvey C, Hughes M, Neoptolemos J. Management of necrotizing pancreatitis. *World J Gastroenterol*, 2001;7(4):476-481

INTRODUCTION

Acute pancreatitis is common, the incidence in recent European studies varying between 20 and 70 cases per 100 000 population with an overall mortality of between 3% and 8%[1-6]. Most cases are secondary to gallstones or excess alcohol consumption. Activation of trypsinogen within pancreatic acinar cells is the critical initiating event[7]. This leads to autodigestion of the pancreas, with a localised and then systemic inflammatory response, which if marked leads to the development of multiple organ dysfunction syndrome (MODS) and death[8,9]. Approximately half of deaths from acute pancreatitis occur in the first week following an attack. In patients who survive the initial attack a proportion develop areas of pancreatic and peripancreatic necrosis. Secondary infection then leads to persisting sepsis, MODS, and accounts for the majority of the remaining late deaths[1,10].

IDENTIFYING PATIENTS WITH NECROSIS

Nearly all patients who suffer a mild attack of acute pancreatitis make a complete recovery[11]. About one third of patients with a severe attack, who develop organ failure during the first week, will however, subsequently develop pancreatic necrosis involving more than 30% of the gland. There are several methods that are routinely used to identify early those patients who are likely to develop organ failure and those who will be at risk of pancreatic necrosis. Specific clinico pathological scoring systems include those described by Imrie[12] and Ranson[13]. These, however, are only accurate 48 hours after hospital admission, when they correctly categorise around 80% of patients into mild and severe. An APACHE II score $\geqslant$9 on hospital admission correctly identifies around 85% patients who will suffer a severe attack[14]. Unfortunately the relative complexity of the APACHE II system limits its clinical use.

Plasma C reactive protein levels (CRP), greater than 150mg/L 48 hours after admission, are widely used to predict a severe attack of pancreatitis[15,16]. CRP levels do not however peak until seventy-two hours after onset of symptoms thus CRP levels, like the Imrie and Ranson scores are limited in predicting a severe attack during the first few hours following admission (Table 1). Plasma levels of other direct inflammatory mediators, such as interleukin-8 and interleukin-6 are elevated earlier in the course of an attack of acute pancreatitis and relate to the severity of the systemic inflammatory response[17]. Although the levels of these mediators are as accurate at the time of admission as the APACHE II score, the assay systems are not suitable for widespread clinical use. Urinary levels of trypsin activation peptide (TAP), the cleavage peptide released following the activation of trypsinogen, become significantly elevated with the onset of an attack and measuring TAP has been shown to be a valuable predictor of severe disease[18] and urinary TAP levels may ultimately form the basis of a simple bedside urine test (Table 1).

Intravenous contrast-enhanced computerised tomography (CE-CT) has also been used to predict the severity of an attack of acute pancreatitis[19]. Balthazar described a CT severity index, based on a combination of peripancreatic inflammation and degree of pancreatic necrosis as seen at initial CT study. Patients with a high CT severity index had 92% morbidity and 17% mortality; patients with a low CT severity index had 2% morbidity, and none died[20]. This type of scoring system using CT offers no advantages as compared to clinico-biochemical scoring systems for the prediction of severe disease[21]. Rather the value of CE-CT is in the detection of pancreatic necrosis and definition of its extent and distribution (Figure 1A)[22-25] as well as in helping to delineate any associated collections[26]. Serial CT scans also allow the progression of the disease to be followed and are an essential adjunct when surgical intervention is required.

Table 1 Prognostic accuracy of the APACHE II, the Imrie and Ranson scores, plasma CRP and urinary TAP levels[18]

Scoring System	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Post-symptom 24 hrs					
Urinary TAP >35nmol/L	58	73	39	86	70
Plasma CRP >150mg/L	0	90	0	75	69
Plasma CRP >150mg/L or urinary TAP >35nmol/L	58	72	37	86	69
Plasma CRP >150mg/L and urinary TAP >35nmol/L	0	92	0	74	70
Post-symptom 48 hrs					
Urinary TAP >35nmol/L	81	71	42	94	73
Plasma CRP >150mg/L	65	73	37	90	72
Plasma CRP >150mg/L or urinary TAP >35nmol/L	86	60	35	94	65
Plasma CRP >150mg/L and urinary TAP >35nmol/L	60	85	50	90	80
Post-hospitalisation 24 hrs					
Urinary TAP >35nmol/L	68	74	44	89	73
Plasma CRP >150mg/L	47	82	42	84	74
Plasma CRP >150mg/L or urinary TAP >35nmol/L	74	66	38	90	68
Plasma CRP >150mg/L and urinary TAP >35nmol/L	40	91	57	83	79
APACHE II ⩾8	63	73	38	88	71
Post-hospitalisation 48 hrs					
Urinary TAP >35nmol/L	83	72	44	94	74
Plasma CRP >150mg/L	86	61	37	94	66
Plasma CRP >150mg/L or urinary TAP >35nmol/L	94	49	32	97	58
Plasma CRP >150mg/L and urinary TAP >35nmol/L	74	85	58	92	83
APACHE II ⩾8	56	64	30	85	63
Imrie Score ⩾3	77	75	44	93	76
Ranson Score ⩾3	89	64	38	96	69

PPV=positive predictive value; NPV=negative predictive value.

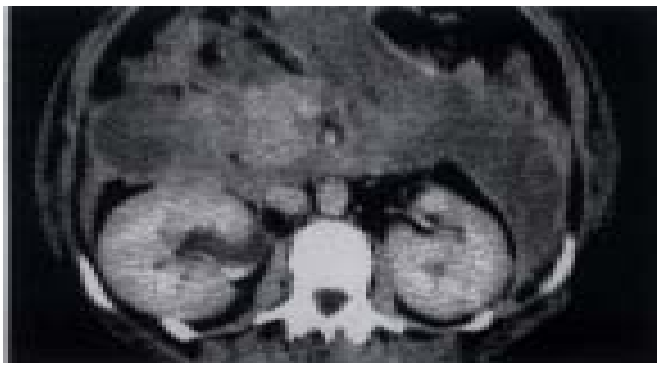

Figure 1A Extensive retroperitoneal pancreatic necrosis.

DETECTION OF INFECTION

In addition to the amount of pancreatic necrosis the outcome in severe pancreatitis is also determined by the presence or absence of infection within the necrotic tissue[27]. Clinical indicators that suggest the presence of infection include pyrexia, hypotension, continuing tachycardia, and a leukocytosis, but these features of sepsis syndrome are identical to those in patients with severe pancreatitis irrespective of the presence of pancreatic infection[28]. Beger *et al* studied 144 patients who underwent open necrosectomy. The proportion of patients who had demonstrable bacterial contamination at the time of necrosectomy increased from 24% during the first week to 36% in the second and peaked at 72% during the third week suggesting that infection is not immediate but that its frequency increases with time[29]. Table 2 shows organisms found within infected necrotic pancreas in their study, which was conducted prior to the routine use of prophylactic antibiotics. The profile of infecting organisms suggests origin from the gastrointestinal tract.

Table 2 Bacteria isolated from operative specimens taken at necrosectomy prior to the introduction of routine antibiotic prophylaxis, Beger *et al*, 1986[29]

Bacteria isolated	No. of patients
Gram - ve aerobic	
Escherichia coli	24
Enterobacter aerogenes	16
Pseudomonas aeruginosa	5
Proteus species	5
Klebsiella pneumonia	3
Citrobacter freundi	1
Gram - ve anaerobic	
Bacteroides species	5
Gram + ve aerobic	
Streptococcus faecalis	6
Staphlococcus aureus	4
Streptococcus viridans	1
Staplococcis epidermidis	1
Others	
Mycobacterium tuberculosis	1
Candida species	3

Several studies have shown that persistently elevated CRP is associated with infected pancreatic necrosis[30]. The presence of gas within an area of necrosis shown by CE-CT is highly suggestive of infection (Figure 1B), although it is desirable to detect the presence of infection before this becomes apparent. CE-CT guided fine needle aspiration, however, allows direct sampling of the necrotic tissue and subsequent microscopy and bacteriology (FNAB) will confirm the presence of infecting organisms (Figure 1C)[31,32].

Figure 1B Infection of pancreatic necrosis with gas forming organisms.

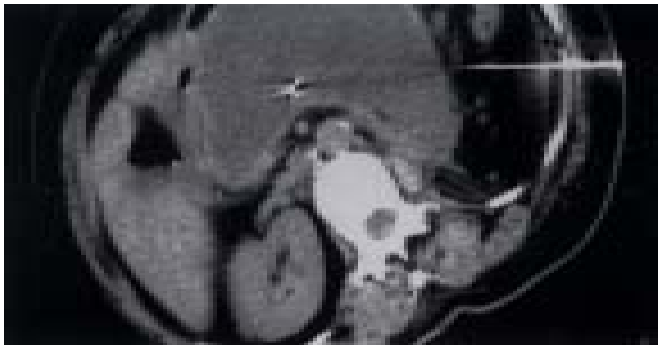

Figure 1C CE-CT guided fine needle aspiration for bacteriology.

The nature of the inflammatory response may also be modified by the presence of infection and recent studies have attempted to identify circulating factors that might confirm this. Serum procalcitonin is a potential marker for non-invasive prediction of infected necrosis[33]. Rau *et al* studied 50 patients with acute pancreatitis, 18 patients with oedematous pancreatitis, 14 patients with sterile necrosis, and 18 patients with infected necrosis. Levels of procalcitonin were measured in plasma during the first two weeks of admission. If levels reached 1.8ng/mL on at least two days during this time, sensitivity, specificity, and accuracy for the prediction of infected necrosis were 94%, 91%, and 92% respectively. This was not confirmed however in a more recent study[34].

PREVENTION OF PANCREATIC NECROSIS

Reducing the severity of the initial attack of acute pancreatitis might reduce the incidence and magnitude of pancreatic necrosis. Unfortunately at the present time, in the absence of effective intervention, management of the acute attack is predominantly supportive. One exception is the use of endoscopic retrograde cholangio-pancreatography and sphincterotomy in patients with predicted severe gallstone pancreatitis, which reduces the severity of an attack. Patients with severe acute pancreatitis due to gallstones need to undergo endoscopic sphincterotomy during ERCP, irrespective of the presence of acute cholangitis and ERCP should be undertaken within forty-eight hours of diagnosis[35-37].

ANTIBIOTIC PROPHYLAXIS

Prophylactic antibiotic use may reduce the incidence of septic complications particularly infection involving areas of pancreatic necrosis. In the 1970s three randomised placebo controlled studies assessed the role of prophylactic antibiotics in acute pancreatitis and found no effect on mortality or morbidity[38-40]. These studies, which were small, consisted almost entirely of patients with mild disease and without necrosis and thus no conclusions can be drawn.

In 1993 Pederzoli *et al* reported a multi-centre randomised study in which 74 patients with pancreatitis from all causes and with confirmed necrosis on CT at the time of admission were randomly assigned to imipenem or to no antibiotic[41]. The incidence of pancreatic sepsis, which was determined by fine needle aspiration or culture of intra-operative specimens, decreased from 30% in those untreated with antibiotics to 12% in the antibiotic treated group. There was, however, no significant difference in the rate of surgical intervention or mortality.

In a subsequent study from Finland, 60 patients with severe alcohol-induced necrotising pancreatitis as determined by CT and CRP estimation were randomly assigned to treatment with cefuroxime or to no antibiotic. One (3%) patient in the antibiotic treated group died compared to seven (23%) patients in the untreated group, ($P<0.05$)[42]. Surprisingly given the large difference in mortality there was no significant difference in the overall incidence of sepsis or the number of patients requiring surgery. Further, given the relatively small size of the study it is probable that there was heterogeneity in the randomisation as shown by the greater number of patients with fulminant pancreatitis on admission in the control group.

More recently, 60 patients with severe acute pancreatitis and necrosis affecting at least 50% of the pancreas, were randomly allocated to receive intravenous treatment for 2 weeks with pefloxacin, (30 patients), or imipenem, (30 patients), within 120 hours of onset of symptoms. The incidence of infected necrosis and extra-pancreatic infections was 34% and 44% respectively in the pefloxacin group and 10% and 20% in the imipenem group. Although imipenem proved significantly more effective in preventing pancreatic infections ($P<0.05$), there was no significant difference in mortality nor in the number of patients requiring surgery between the two treatments[43]. A feature of this last study and of other recent series[44,45] in which prophylactic antibiotics have been used is the increasing incidence of drug resistant or unusual organisms, including fungi, cultured from pancreatic tissue removed at necrosectomy. When such organisms are present the mortality following necrosectomy may be increased[46,47]. Thus the data imply that the use of prophylactic antibiotics promotes drug-resistant organisms and the growth of fungi. In the absence of further studies routine antibiotic prophylaxis in patients with acute pancreatitis cannot be recommended at present.

TRANSLOCATION OF GUT ORGANISMS

The gastrointestinal tract is thought to be the major source of organisms infecting necrotic pancreatic tissue. Increased translocation of bacteria and toxins is known to occur in acute pancreatitis[48,49]. Anaerobic bacteria are less likely to translocate from the gut lumen. Thus selective digestive decontamination (SDD) with appropriate antibiotics may change the intestinal flora to one that is less invasive. Between 1990 and 1993, 102 patients with severe pancreatitis from 16 centres in the Netherlands were randomized to selective digestive decontamination plus standard treatment or standard treatment alone[50]. There was a significant reduction in the incidence of gram-negative pancreatic infection in treated patients. Although deaths were reduced from 35% in the control group to 22% in the treatment group this difference was not significant. A short course of systemic antibiotics (cefotaxime) was used in the SDD group so that interpretation of the data with regard to the specific effects of gut decontamination as opposed to antibiotic prophylaxis is difficult[50].

Early re-introduction of nutrition via the gastrointestinal tract may also help to restore mucosal integrity and reduce translocation. A number of studies in patients with major trauma, surgery and burns showed that enteral nutrition significantly decreased the acute phase response and incidence of septic complications when compared with total parenteral nutrition[51,52]. In acute pancreatitis therefore early reintroduction of feeding via the gastro intestinal tract might also reduce the incidence of pancreatic infection.

Two randomized studies have compared enteral and parenteral nutrition in patients with severe acute pancreatitis. In the first study, 38 patients received enteral nutrition through a nasoenteric tube with a semi-elemental diet or parenteral nutrition through a central venous catheter. Patients who received enteral feeding experienced fewer total complications ($P<0.05$) and were at lower risk of developing septic complications ($P<0.01$) than those receiving parenteral nutrition. The cost of nutritional support was three times higher in patients who received parenteral nutrition[53].

In a second study from Leeds, 34 patients with acute pancreatitis received either parenteral or enteral nutrition for seven days and were then re-evaluated. The frequency of SIRS, sepsis, organ failure and the need for ITU admission was reduced in the enterally fed patients[54].

In a third study from Edinburgh, 27 patients with predicted severe acute pancreatitis were randomised to early introduction of enteral nutrition via a nasojejunal tube or conventional therapy, i.e. nil by mouth with re-introduction of oral intake with return of gut function. There were no significant complications as a consequence of enteral nutrition. The introduction of enteral nutrition did not affect the serum concentrations of IL-6 (P=0.28), soluble tumour necrosis factor-α receptor (P=0.53) or CRP (P=0.62) over the first 4 days of the study. Although there were no significant differences in intestinal permeability between the two patient groups at admission, by day four abnormal intestinal permeability occurred more frequently in patients receiving enteral nutrition (P=0.03).

Thus it can be concluded that enteral nutrition is safe in patients with severe acute pancreatitis and there is some evidence that it may be preferable to parenteral nutrition. The power of these three studies was too low to show any differences with respect to surgical intervention, incidence of pancreatic infection or mortality and the effect of nutrition route and timing on these outcomes requires further study.

NON-OPERATIVE TREATMENT OF PANCREATIC NECROSIS

Although there are isolated case reports of patients with pancreatic infection surviving with medical treatment alone[55] and limited success using percutaneous drainage[56,57], the presence of infection in necrotic pancreatic tissue is accepted to be an absolute indication for surgical intervention (Table 3). The situation in patients with extensive areas of sterile necrosis is less clear. Bradley *et al* reported on 38 patients with necrosis on CT who were initially treated medically and underwent FNAB if they remained persistently febrile. Infected pancreatic necrosis was demonstrated in 27 (71%) of the 38 patients with pancreatic necrosis who were treated by open drainage, with a mortality rate of 15%. All 11 patients with sterile pancreatic necrosis, including six with pulmonary and renal insufficiency, were successfully treated without surgery[58]. On the basis of this and subsequent studies sterile necrosis, should initially be managed non-operatively[59].

Table 3 Indications for surgical intervention

Absolute	• Presence of infected pancreatic necrosis shown by CE-CT or FNAB.
Relative	• In a patient with >50% pancreatic necrosis, failure to improve appreciably after 2 - 3 weeks, unexplained deterioration, or a suspicion of infected pancreatic necrosis even in the absence of firm evidence on CE-CT and FNAB. In a patient with >50% pancreatic necrosis, • prolonged illness with an unacceptably slow recovery

The optimal frequency of CE-CT imaging and FNAB has not been clearly established. In the recent study from Bern, all patients underwent contrast-enhanced CT within 24 to 48 hours of admission and this was repeated weekly in those patients whose clinical condition did not improve[45]. Fine needle aspiration under CT guidance with subsequent microscopy and bacteriological culture was undertaken to rule out infection in patients who developed signs of metabolic disorders, those with deteriorating function of lung, kidney or the cardio circulatory systems and those with persistent leukocytosis or fever (>38.5℃).

A second issue is the treatment of patients with sterile necrosis who remain unwell. In this group surgical intervention has been suggested for patients with persisting or advancing organ complications despite intensive care therapy[59]. In contrast in a recently published single-centre study, pancreatic infection, if confirmed by fine-needle aspiration, was considered an indication for surgery, whereas patients without signs of pancreatic infection were treated medically[45]. Eighty-six (42%) of the patients in this study had necrotizing disease, of which two thirds had sterile necrosis. The death rate was 1.8% (1/56) in patients with sterile necrosis managed without surgery versus 24% (7/29) in patients with infected necrosis (P<0.01). Two patients whose infected necrosis was not diagnosed in time died whilst receiving medical treatment. Thus, an intent to treat analysis (non-surgical *vs.* surgical treatment) produced a death rate of 5% (3/58) with conservative management versus 21% (6/28) with surgery. The authors concluded that non-surgical management, including early antibiotic treatment, should be used in all patients with sterile pancreatic necrosis[45]. In contrast other authors have observed a similar mortality in patients undergoing necrosectomy between those with sterile and those with infected necrosis[60].

TIMING OF SURGERY

Timing of surgery is critical. Necrosectomy is technically difficult during the first week but becomes progressively easier with time. One controlled trial has addressed the role of early surgery. Forty-one patients with pancreatic necrosis on CT were randomized to early necrosectomy (within 48 to 72 hours of onset) or late necrosectomy (at least 12 days after onset). Both groups continued with open packing and staged necrosectomies. Although the mortality rate (58% versus 27%) did not reach statistical significance, the odds ratio for mortality was 3.4 times higher in the early group and for this reason the study was terminated early[61]. Thus the contemporary management of patients with extensive necrosis involves repeated imaging using contrast-enhanced CT in association with fine needle aspiration for microscopy and bacteriology with immediate surgery if infection is detected.

OPEN NECROSECTOMY

Necrosectomy has traditionally been undertaken by an open route. Following laparotomy the lesser sac is opened if possible, the colon is mobilised downwards and the pancreas identified. Necrotic pancreas is debrided by blunt finger dissection and wide bore suction drainage. If opening of the lesser sac is not possible, direct access from the infracolic compartment via the left transverse mesocolon (space of Riolan) is an alternative. Adequate debridement is usually achieved with a single visit to theatre. Any associated fluid collections are drained by the most direct route. Large drains and irrigating catheters are left within the retroperitoneal area and continuous irrigation is continued post surgery[62]. The use of open packing with multiple visits to theatre prior to secondary closure over drains has been described but hospitalisation can be significantly reduced by using prolonged lavage rather than pre-planned multiple laparotomies. Mortality rates in recent series are generally between 20%-40%[45,58,60-67], but may be higher even in specialised centres[33].

Several developments have led to a reassessment of the role and the extent of surgery in acute pancreatitis. Percutaneous drainage has been advocated as a means of

treating pancreatic necrosis[56,57,68]. Unfortunately it is impossible to achieve adequate debridement of solid pancreatic debris by this route except in a minority of cases and it may lead to secondary infection in pancreatic necrosis that is initially sterile. Aggressive percutaneous drainage has been proposed as a means of treating infected pancreatic necrosis. A major reason for failure however is the variable amounts of infected solid material that cannot be removed. Indeed Paye *et al* [69] found percutaneous drainage to be largely inadequate requiring surgical intervention in the majority of cases.

In an attempt to reduce the high mortality from surgical necrosectomy less traumatic approaches than open laparotomy have been advocated. Fagniez *et al*[70] described a retroperitoneal approach for pancreatic necrosectomy through the left flank just anterior to the 12th rib. There was an overall mortality of 33% in 40 patients with severe pancreatic necrosis and 18% in the 22 patients in whom this was the only abdominal procedure performed. Similarly good results have been reported in three other small series[71-73]. Morbidity rates, including colonic fistulae and haemorrhage were, however, high.

Another factor that has led to the re-evaluation of the extent of surgery has been the concept of the two-hit response. This hypothesis states that many patients with a severe attack of acute pancreatitis are primed to mount an inappropriate and exaggerated inflammatory response to a second traumatic challenge[8,9]. Thus a subsequent hit, for example from an open procedure to debride the infected necrotic pancreas, may lead to an overwhelming systemic inflammatory response and death. This would account in part for the continuing high mortality that follows open surgical necrosectomy. Unfortunately patients liable to have such an abnormal response cannot be identified at present although markers of genetic susceptibility are being sought.

A new technique of minimally invasive pancreatic necrosectomy via a left loin approach, analogous to the open technique of Fagniez *et al*[70] was recently pioneered in Glasgow[74]. The advantages of this technique are two-fold. First the peritoneal cavity is not transgressed, and second, tissue damage is limited-thus reducing the magnitude of the systemic inflammatory response of the second hit. Mortality in the 10 patients treated by this technique was only 20%. We have used this technique in a further 14 patients with 3 (21%) deaths[75]. We believe that these results are encouraging and that in the future a significant proportion of patients with infected pancreatic necrosis may be managed by this technique.

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Edited by Rampton DS and Ma JY