World J Surg (2012) 36:1142–1147
DOI 10.1007/s00268-012-1504-5

World Journal of Surgery

Treatment of Necrotizing Pancreatitis: Redefining the Role of Surgery

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Published online: 2 March 2012

Abstract
Background Early surgical intervention in necrotizing pancreatitis (NP) is associated with high mortality. Guidelines recommend fine needle aspiration (FNA) in patients with NP and signs of sepsis. Because infection of necrosis is considered an indication for surgery, operations are often performed early. We changed treatment toward a conservative approach with FNA in selected cases only, thereby reducing the rate of necrosectomy.
Methods Retrospectively analyzed patients, all operated on for FNA-proven infection of pancreatic necrosis ($n = 20$, group 1) were compared to patients subjected to conservative treatment ($n = 24$, group 2) who were followed prospectively.
Results Prognostic scores did not differ between the two groups, indicating comparable severity: the Acute Physiology and Chronic Health Evaluation (APACHE II) score was 19.8 ± 1.7 versus 16 ± 2.2; the Sequential Organ Failure Assessment (SOFA) score was 8.7 ± 1.4 versus 6.9 ± 1.0, the C-reactive protein (CRP) level on day 3 was 243 ± 21 versus 291 ± 21, and the CTSI (CT severity index) was 7.8 ± 0.5 versus 7.9 ± 0.4 ($p = $ ns). Ten patients in group 2 underwent operation because of severe extrapancreatic complications. Mortality differed significantly (45% in group 1 vs. 8.3% in group 2; $p = 0.01$).
Conclusions A highly conservative approach avoiding open necrosectomy in NP results in significantly lower mortality than previous serial FNA and consecutive indication for surgery in case of proven infection. Open surgery in NP should be reserved for concomitant intra-abdominal complications.

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Introduction

The mortality of patients with necrotizing pancreatitis has gradually declined over recent decades with improved diagnostic methods and treatment modalities [1, 2]. Treatment principles of necrotizing pancreatitis and the role of surgery are still controversially discussed. Twenty years ago more than 60% of patients with the disease were treated surgically [3]. In 1991 Bradley and Allen [4] defined pancreatic necrosis as the principal determinant of survival in acute pancreatitis, but they recommended conservative treatment of sterile necrosis in selected cases. Guidelines of the International Association of Pancreatology (IAP) recommend performance of fine needle aspiration (FNA) in patients with necrotizing pancreatitis and signs of sepsis. Once FNA-proven infection of necrosis has been shown, it is considered indication for operative intervention [5]. In addition, timing of surgery has been increasingly recognized as a major determinant of outcome in acute pancreatitis, and there is now general agreement that patients should undergo operation in the late phase of the disease. However, the definition of "late" differs considerably between studies [5, 6].

In the present study we tried to optimize the treatment strategy for necrotizing pancreatitis with regard to indications for operation and the role of fine needle aspiration. We focused on the effect of operative intervention in the

course of necrotizing pancreatitis. The aim of the study was to evaluate the effect of the maximum conservative treatment algorithm with delayed surgical intervention and a highly restricted use of FNA compared to a historical control group subjected to surgical necrosectomy based on positive FNA.

Patients and methods

In the Department of Surgery, University of Rostock, different treatment strategies were subsequently applied over the last years. After the introduction of a new department chairman, data of patients with necrotizing pancreatitis were prospectively collected from 09/2003 to 12/2007 (group 2) and were compared to a retrospectively analyzed group of patients treated earlier (03/2000–08/2003, group 1). Definitions according to the Atlanta classification were used [7]. Inclusion criteria were >8 APACHE II points, >3 Ranson signs, and presence of one or more organ failures and/or presence of local complications as described by Bradley [7]. All patients required ICU treatment, which did not differ between groups.

Before the introduction of a new treatment algorithm, all patients with NP and signs of sepsis had fine needle aspiration (FNA) of pancreatic necrosis. The FNA studies were repeated weekly, and if the FNA cytology was positive, the patient was referred for pancreatic necrosectomy. With this regimen virtually all patients in our department underwent operation. To compare the effect of surgical intervention in necrotizing pancreatitis, these patients were analyzed as group 1.

The approach to prospectively collected patients (group 2) differed, as they were treated conservatively after an initial stabilization period of up to 72 h without FNA. An initial CT scan for evaluation of the extent of pancreatic necrosis was performed during that time, as well. Only clinical deterioration despite maximum intensive care was an indication for surgical intervention. If patients could be stabilized by ICU therapy, there was no operative intervention, even in the case of multiple organ failure (MOF). No routine FNA studies were performed. Treatment was primarily conservative in nature unless there were clinical signs of acute abdomen or other secondary complications that required surgical or radiological intervention.

In both groups the following scores and prognostic markers were assessed: the CRP level and the APACHE II and SOFA score were assessed for the first 7 days; the Ranson score upon primary admission and the CTSI score based on the index CT performed within the first 72 h were also assessed. Organ failure was defined according to the Atlanta classification [7]. Organ failure and radiological and surgical interventions were documented. The incidence of organ failure represents the summary of organ dysfunction throughout the entire hospital stay. Moreover, the body mass index of all patients was calculated, and type and timing of nutrition was compared.

During the entire time period of our study (groups 1 and 2) ICU management remained unchanged. Thereafter, personnel and structural changes occurred. Therefore all patients admitted at a later time point were excluded from this study. Data are presented as mean ± SEM. Differences between groups were compared using Student's *t* test, the Mann–Whitney *U* test, or Fisher's exact test, where applicable. Data were analyzed with GraphPad Prism (version 4.00 for Windows; GraphPad Software, San Diego CA).

Results

Twenty patients were identified from 03/2000 through 08/2003 who were operated following positive FNA and were analyzed as group 1. Group 2 consisted of 24 consecutive patients with necrotizing pancreatitis. 22 of whom were primarily admitted to our department, and two patients were transferred within 24 h after onset of the disease between 09/2003 and 12/2007.

Table 1 summarizes the clinical characteristics of both groups. All prognostic parameters and parameters describing the severity of the disease in both groups, including organ

Table 1 Comparison of characteristics, prognostic scores, and overall mortality of the two study groups

Parameter	Group 1 $n = 20$	Group 2 $n = 24$	*p* Value
Age	55.1 ± 3.4	55 ± 3.4	0.992
Body mass index	30 ± 1.6	27.1 ± 0.7	0.126
Male	7	6	NA
Female	13	18	NA
APACHE II upon admission[a]	19.8 ± 1.7	16.1 ± 1.9	0.169
SOFA upon admission[a]	8.7 ± 1.4	6.9 ± 1.0	0.312
Ranson score	3.9 ± 0.3	3.9 ± 0.2	0.305
CTSI index CT	7.8 ± 0.5	7.9 ± 0.4	0.803
CRP on day 3 (mg/dl)[a]	243 ± 21	291 ± 21	0.116
3-Organ failure[b]	30%	46%	0.467
2-Organ failure[b]	5%	8.3%	0.662
1-Organ failure[b]	0%	4.2%	0.356
Enteral feeding of patients	75%	96%	NA
Overall mortality	45%	8.3%	0.01

CTSI CT severity index, *CRP* C-reactive protein, *APACHE II* Acute Physiology and Chronic Health Evaluation score, *SOFA* Sequential Organ Failure Assessment

[a] APACHE II and SOFA scores and CRP were evaluated daily for the first 7 days without statistical difference on any day

[b] Describes amount of organ failure of the entire hospital stay, not only upon admission. Data are presented as mean ± SEM

failure, were comparable at all times. Only in-hospital mortality significantly differed between groups (8.3% vs. 45%; $p = 0.01$). Operations and interventions in the two groups are summarized in Table 2. In group 1 a total of 49 programed FNAs were performed and led to operation within the first 3 weeks in 12 patients. Indication for surgery in all patients was a positive FNA. In 10 patients programed abdominal reintervention with lavage was performed. Only four patients needed one operation with no reintervention, all others required at least one re-laparotomy. In five patients additional colonic resections had to be performed as a result of bowel ischemia. In the 20 patients a total of 144 operations were performed. The median number of operations was 4.5 per patient. Only one patient received interventional radiological abscess drainage. Overall mortality in this group was 45%.

In group 2 four patients (16.6%) required early and immediate surgery for severe complications (duodenal perforation, fulminant gangrene of the entire colon, peritonitis, and development of a symptomatic incarcerated inguinal hernia). Of these four patients, one required pancreatic debridement during the first operation, and in two others debridement was performed in a second or third operation after management of the initial complications. Pancreatic necroses or intra-abdominal cultures in all four of these patients were positive for bacteria. One patient died on day 64. Twenty patients were treated conservatively for at least 3 weeks after a successful stabilization period of 3 days. Six of these 20 patients developed secondary complications—i.e., colonic perforations, ileus, or enterocutaneous fistulas—and therefore underwent surgery. In 3 of these 6 patients pancreatic debridement was performed during the same operation. None of the 6 patients died. In all operated patients intra-abdominal cultures and/or pancreatic necroses were positive for bacteria. Fourteen patients were managed by conservative means only, and one of them died on day 59 after the onset of NP (age 89 years). In this patient one FNA was performed, and the result was negative. Deterioration of the patient's clinical condition with progression of MOF resulted in CT-guided drainage and culture, which was positive. Despite efficient decompression of the lesser sac, the patient rapidly deteriorated and died. In two of these 14 patients CT-guided drainage of peripancreatic fluid collections was performed. In one, abscess formation was suspected on CT, and the other patient went on to develop respiratory insufficiency as a result of expanding peripancreatic fluid collection. The cultures of both patients were positive, yet both recovered after CT-guided drainage and subsequent continuous lavage without operation. Four patients received CT-guided drainage of intra-abdominal abscesses. Positive FNA was not the indication for operation in any of the patients in group 2 who underwent operation. Overall, 31 operations were performed. (The median number of operations was 0 per patient.) Comparing all operations between the two study groups, the actual numbers differed significantly ($p < 0.001$). In summary, 5 of 24 patients in this group underwent 5 FNAs. Nine patients did not have FNA, drainage, or operation. Comparing all prognostic scores between these 9 patients and all other patients in group 2, no statistically significant differences were observed (Table 3). Two patients of group 2 died (mortality 8.3%).

Nutritional support differed between the study groups: 23 patients in group 2 received enteral nutrition (96%), but

Table 2 Comparison of different treatment characteristics of the two groups

	Group 1	Group 2
Patients (*n*)	20	24
FNA	49	5
No prior operation (total number)		
Operations (total number)	144	31
Median number of operations	4.5	0
Indications of operation	Positive FNA ($n = 20$) (Gangrene of colon; $n = 5/20$)	Duodenal perforation ($n = 1$) Gangrene of colon ($n = 1$) Peritonitis ($n = 1$) Incarcerated inguinal hernia ($n = 1$) Colonic perforation ($n = 3$) Abscess ($n = 1$) Enterocutaneous fistula ($n = 1$) Ileus ($n = 1$)
Percentage of patients where necrosectomy was performed	100%	25% ($n = 6$)
CT drainage of intra-abdominal abscess	1	4
CT-guided placement of lavage catheters	0	6

FNA fine-needle aspiration cytology

Table 3 Subgroup analysis of study group 2, with detailed analysis of prognostic scores, interventions, and status of infection

Group 2 ($n = 24$)	Conservative treatment—no intervention at all	Patients with intervention or operation	Comparison of severity, p value
Patients (n)	9	15	
Patients died (n)	0	2	
FNA sterile	NA	3	
FNA positive	NA	3	
Infected pancreatic necrosis/ positive abdominal culture	NA	9	
APACHE II score upon admission	14.6 ± 3.4	16.8 ± 2.5	0.585
SOFA score upon admission	5.9 ± 1.6	7.9 ± 1.4	0.369
Ranson score	3.8 ± 1.6	4.1 ± 0.1	0.553
CTSI index CT	8.1 ± 0.7	7.8 ± 0.5	0.705
CRP on day 3 (mg/dl)	264 ± 28	306 ± 28	0.344

Severity of disease in nine patients without operation or intervention is comparable to all other patients. Indications and total number of operations and interventions are compared

only 15 patients in group 1 (75%) did. Enteral feeding was initiated significantly earlier in group 2 than in group 1 (on day 3.3 ± 0.5 vs. day 7.0 ± 1.4; $p = 0.02$). In addition, 22 patients in group 2 (92%) and 19 patients in group 1 (95%) received parenteral nutrition. Parenteral nutrition in group 2 was started on day 2.5 ± 0.4 after admission and in group 1 on day 1.5 ± 0.5 (ns).

Discussion

The main finding of our study is that mortality from necrotizing pancreatitis can be profoundly reduced by avoiding surgical therapy or by postponing surgical treatment to the late stage of the disease. This concept is based on clinical decision making, together with a restriction of FNA. Without the FNA testing, we were not evaluating whether pancreatic necroses were infected or not. In this series 92% of patients had extended necrosis involving more than 50% of the pancreatic parenchyma, which was reflected by a mean CTSI score of 8. The overall severity of the disease was documented by three-organ failure in 46% of patients and a mean APACHE II score of 16 on admission. We did not comply with the guidelines of the International Association of Pancreatology (IAP) [5]. Even if patients had early three-organ failure but did not deteriorate, we continued ICU therapy without performing FNA. Mortality among the 24 patients treated according to this concept was 8.3%.

This prospective observational study was triggered by a retrospective analysis of 20 patients with necrotizing pancreatitis at our institution in whom FNA was performed according to the IAP-guidelines [5]. In that series of patients, if signs of sepsis were present, debridement was performed in cases of infection. According to this protocol, necrosectomy was performed in all patients, and the mortality rate was 45%.

Comparing the two treatment concepts, the first conclusion is that mortality is high if pancreatic necrosectomy is performed. This statement challenges the IAP guideline recommendation that FNA should be performed in the presence of signs of sepsis. Clinical systemic inflammatory response syndrome (SIRS) or sepsis is often encountered in the early stage of acute pancreatitis, and this has led to FNA which, by definition, leads to debridement if infection is detected at any point during the time course of the disease. Because of extended necroses and equal severity of pancreatitis in patients who have undergone early operation, we began to avoid operation and were able to do so entirely in the majority of patients, and to postpone surgical intervention beyond the third week in group 2. The main treatment target remained MOF, which resulted in intensive care treatment rather than surgical intervention, as early MOF is a major risk factor for death in severe acute pancreatitis [8]. Three points are noteworthy in group 2:

(1) None of the six patients who underwent operation were treated with the aim to debride the pancreatic necrosis, but rather to treat complications affecting adjacent extrapancreatic structures. Because intra-abdominal infection was present, and because the superinfection associated with pancreatic necrosis could be expected, concomitant necrosectomy was performed in 50% of those patients. In contrast, in group 1 all patients were operated on with the primary goal of necrosectomy. 2. We cannot define the incidence of infected pancreatic necrosis among 9 patients of group 2 who were treated conservatively without any intervention. However, Isenmann et al. [9] have shown that the extent of necrosis correlates with the incidence of infection. In our cohort 98% of patients had >50% pancreatic necrosis. Therefore, it is very likely that a certain percentage had infection and were treated conservatively, an approach that has proven feasible according to Rünzi et al. [10].

(2) Although the severity of disease was comparable in patients treated conservatively and patients treated surgically, the main limitation of our study is that we did not account for the state of infection in most of the patients treated conservatively because we had established the basic clinical concept which profoundly restricted the performance of FNA.
(3) In parallel with the reduction of operative treatment, the need for radiological interventions increased. The catheter techniques employed were primarily directed at drainage of fluid collections, including abscesses, and not at interventional necrosectomy. However, in five patients the catheters placed by CT guidance were also used for subsequent lavage. In contrast, in group 1, CT drainage was performed in one patient only.

Büchler et al. have shown that organ failure and severity of acute pancreatitis is reduced with sterile necrosis, resulting in the broad agreement among clinicians that necroses in the absence of infection should be treated conservatively [4, 11–13]. According to our data, patients with necrotizing pancreatitis seem to benefit from conservative treatment despite extended necrosis and MOF. This treatment protocol requires that the patient, although critically ill, can be maintained in a stable condition by ICU therapy. In a certain percentage of patients intra-abdominal complications outside the pancreas will necessitate operative treatment. In group 2 in our study, patients underwent operation for the treatment of intra-abdominal complications during weeks 4–6 after disease onset. Fernandez-del Castillo et al. defined a group of patients with different characteristics of "ongoing pancreatitis" necessitating debridement beyond the seventh week. These patients, who were in stable condition and had low APACHE II scores, were confined to the hospital because they could not tolerate oral feeding and failed to recover [14]. If patients with severe pancreatitis are to be operated on less and later, it seems important to systematically evaluate subgroups that will benefit from an "elective" debridement in the post-acute phase which may be facilitated by a retroperitoneal minimally invasive operative approach.

As in our study, Besselink et al. [15] could also demonstrate that postponing necrosectomy until 30 days after admission could decrease mortality. One published controlled clinical trial could show that indeed a minimally invasive approach can reduce major complications. However, no difference in mortality was noted in this study [16]. A recently published study from India compared initial conservative treatment of infected pancreatic necrosis versus necrosectomy. However, the mortality rate among conservatively treated patients was comparable to that for primarily operated patients. Interestingly, operation could be avoided in 76% of patients with infected necrosis [17].

Other investigators and our group have previously shown that mortality of patients with necrotizing pancreatitis has decreased significantly over the past decades [1, 2, 4, 18, 19], chiefly because surgery was carried out less frequently and later in the course of the disease.

In order to evaluate other factors that might account for the different mortality rates in our two study groups, we compared body mass index and nutritional support. Obesity is a prognostic factor favoring the development of complications [20], but body mass index was comparable in the two study groups. Benefit of enteral nutrition on the course of necrotizing pancreatitis was demonstrated by other investigators [21, 22]. In our two groups, the data for enteral feeding were not significantly different, but enteral feeding was started significantly earlier in group 2.

Conclusions

Necrosectomy during the early stage of acute pancreatitis should be avoided because it has been associated with high mortality rates. Therefore FNA must be restricted to the late phase of the disease where it may aid decision making in selected patients who have not experienced clinical improvement.

Detection of infection is irrelevant as long as the patient remains clinically stable even in the presence of MOF. If the clinical condition, especially concerning cardiovascular function, deteriorates, operation may be the only option regardless of the status of infection of pancreatic necrosis. With this less aggressive treatment protocol, the need for catheter drainage of fluid collection or abscess increases. Secondary intra-abdominal complications might necessitate surgical therapy and the indication for operation is thus shifted away from classical debridement. It appears likely that infected pancreatic necrosis is not an absolute indication for operation in clinically stable patients. However, conservative management of infected pancreatic necrosis has not been sufficiently evaluated yet, and a prospective randomized study is still needed.

References

1. Hartwig W, Maksan SM, Foitzik T et al (2002) Reduction in mortality with delayed surgical therapy of severe pancreatitis. J Gastrointest Surg 6:481–487
2. Warshaw AL (1993) Damage prevention versus damage control in acute pancreatitis. Gastroenterology 104:1216–1219
3. Beger HG, Buchler M, Bittner R et al (1988) Necrosectomy and postoperative local lavage in necrotizing pancreatitis. Br J Surg 75:207–212
4. Bradley EL III, Allen K (1991) A prospective longitudinal study of observation versus surgical intervention in the management of necrotizing pancreatitis. Am J Surg 161:19–24

5. Uhl W, Warshaw A, Imrie C et al (2002) IAP Guidelines for the Surgical Management of Acute Pancreatitis. Pancreatology 2:565–573
6. Hungness ES, Robb BW, Seeskin C et al (2002) Early debridement for necrotizing pancreatitis: Is it worthwhile? J Am Coll Surg 194:740–744
7. Bradley EL III (1993) A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, GA, September 11–13, 1992. Arch Surg 128:586–590
8. Rau BM, Bothe A, Kron M et al (2006) Role of early multisystem organ failure as major risk factor for pancreatic infections and death in severe acute pancreatitis. Clin Gastroenterol Hepatol 4:1053–1061
9. Isenmann R, Rau B, Beger HG (1999) Bacterial infection and extent of necrosis are determinants of organ failure in patients with acute necrotizing pancreatitis. Br J Surg 86:1020–1024
10. Rünzi M, Niebel W, Goebell H et al (2005) Severe acute pancreatitis: nonsurgical treatment of infected necroses. Pancreas 30:195–199
11. Buchler MW, Gloor B, Muller CA et al (2000) Acute necrotizing pancreatitis: treatment strategy according to the status of infection. Ann Surg 232:619–626
12. Werner J, Feuerbach S, Uhl W et al (2005) Management of acute pancreatitis: from surgery to interventional intensive care. Gut 54:426–436
13. Heinrich S, Schafer M, Rousson V et al (2006) Evidence-based treatment of acute pancreatitis: a look at established paradigms. Ann Surg 243:154–168
14. Fernandez-del Castillo C, Rattner DW, Makary MA et al (1998) Debridement and closed packing for the treatment of necrotizing pancreatitis. Ann Surg 228:676–684
15. Besselink MG, Verwer TJ, Schoenmaeckers EJ et al (2007) Timing of surgical intervention in necrotizing pancreatitis. Arch Surg 142:1194–1201
16. van Santvoort HC, Besselink MG, Bakker OJ et al (2010) A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med 362:1491–1502
17. Garg PK, Sharma M, Madan K et al (2010) Primary conservative treatment results in mortality comparable to surgery in patients with infected pancreatic necrosis. Clin Gastroenterol Hepatol 8:1089–1094
18. Rau B, Bothe A, Beger HG (2005) Surgical treatment of necrotizing pancreatitis by necrosectomy and closed lavage: changing patient characteristics and outcome in a 19-year, single-center series. Surgery 138:28–39
19. Pederzoli P, Bassi C, Vesentini S et al (1993) A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. Surg Gynecol Obstet 176:480–483
20. Martinez J, Sanchez-Paya J, Palazon JM et al (2004) Is obesity a risk factor in acute pancreatitis? A meta-analysis. Pancreatology 4:42–48
21. Petrov MS, Kukosh MV, Emelyanov NV (2006) A randomized controlled trial of enteral versus parenteral feeding in patients with predicted severe acute pancreatitis shows a significant reduction in mortality and in infected pancreatic complications with total enteral nutrition. Dig Surg 23:336–344
22. Marik PE, Zaloga GP (2004) Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. BMJ 328(7453):1407