

# CLINICAL—PANCREAS

## A Conservative and Minimally Invasive Approach to Necrotizing Pancreatitis Improves Outcome

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This article has an accompanying continuing education activity on page e23. Learning Objective: Upon completion of this CME exercise, successful learners will be able to identify the most common indications for intervention in necrotizing pancreatitis and point out the patient's prognosis according to type and indication for intervention.

See Covering the Cover synopsis on page 1133.

**BACKGROUND & AIMS:** Treatment of patients with necrotizing pancreatitis has become more conservative and less invasive, but there are few data from prospective studies to support the efficacy of this change. We performed a prospective multicenter study of treatment outcomes among patients with necrotizing pancreatitis. **METHODS:** We collected data from 639 consecutive patients with necrotizing pancreatitis, from 2004 to 2008, treated at 21 Dutch hospitals. Data were analyzed for disease severity, interventions (radiologic, endoscopic, surgical), and outcome. **RESULTS:** Overall mortality was 15% (n = 93). Organ failure occurred in 240 patients (38%), with 35% mortality. Treatment was conservative in 397 patients (62%), with 7% mortality. An intervention was performed in 242 patients (38%), with 27% mortality; this included early emergency laparotomy in 32 patients (5%), with 78% mortality. Patients with longer times between admission and intervention had lower mortality: 0 to 14 days, 56%; 14 to 29 days, 26%; and >29 days, 15% (P < .001). A total of 208 patients (33%) received interventions for infected necrosis, with 19% mortality. Catheter drainage was most often performed as the first intervention (63% of cases), without additional necrosectomy in 35% of patients. Primary catheter drainage had fewer complications than primary necrosectomy (42% vs 64%, P = .003). Patients with pancreatic parenchymal necrosis (n = 324), compared

with patients with only peripancreatic necrosis (n = 315), had a higher risk of organ failure (50% vs 24%, P < .001) and mortality (20% vs 9%, P < .001). **CONCLUSIONS: Approximately 62% of patients with necrotizing pancreatitis can be treated without an intervention and with low mortality. In patients with infected necrosis, delayed intervention and catheter drainage as first treatment improves outcome.**

**Keywords:** Pancreas; Inflammation; Treatment; Surgery; Clinical Trial.

Acute pancreatitis is complicated by necrosis of the pancreatic parenchyma and/or the peripancreatic fat tissue in approximately 20% of patients.<sup>1,2</sup> The clinical course of necrotizing pancreatitis can be divided into 2 phases. In the first phase (ie, 1–2 weeks after onset of symptoms), a systemic inflammatory response syndrome occurs, which is often associated with multiple organ failure.<sup>3–5</sup> Interventions in the first phase are relatively

**Abbreviations used in this paper:** APACHE II, Acute Physiology and Chronic Health Evaluation II; ASA, American Society of Anesthesiologists; CECT, contrast-enhanced computed tomography; CT, computed tomography; ETN, endoscopic transluminal necrosectomy; IQR, interquartile range; VARD, video-assisted retroperitoneal debridement.

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contraindicated, although some patients require an emergency laparotomy for complications such as abdominal compartment syndrome or bowel ischemia.<sup>3</sup> It has been suggested that approximately half the deaths from necrotizing pancreatitis are caused by multiple organ failure in the early phase.<sup>6,7</sup> In the late phase of the disease (ie, after 1–2 weeks), systemic inflammation often regresses and infected necrosis occurs in about 30% of patients with necrotizing pancreatitis.<sup>8,9</sup> Without radiologic, endoscopic, or surgical intervention, infected necrosis ultimately leads to death in nearly every patient.

Treatment of necrotizing pancreatitis has changed considerably over the years. First, the indication for intervention has shifted. Whereas historically most patients with sterile necrosis underwent necrosectomy, it is now accepted that sterile necrosis should largely be managed conservatively and that the main indication for intervention is infected necrosis.<sup>3,10–12</sup> Second, the timing of intervention has changed. Necrosectomy was once performed at a very early stage,<sup>13</sup> but now it is believed that intervention should be delayed to approximately 3 to 4 weeks after onset of disease.<sup>14–16</sup> This time frame allows for encapsulation of peripancreatic collections, which may improve conditions for intervention and thereby decrease the risk of complications such as bleeding and perforation. Third, as an alternative to the historical standard of primary open necrosectomy,<sup>17</sup> minimally invasive techniques, such as percutaneous catheter drainage and minimally invasive necrosectomy, are increasingly used.<sup>18–24</sup>

The outcome of patients with necrotizing pancreatitis after the recent implementation of the previously mentioned changes is unknown. Although several cohort studies on necrotizing pancreatitis have been published over the past decades,<sup>9</sup> these data are outdated and of limited clinical relevance for several reasons. First, these studies mostly did not include patients with peripancreatic necrosis only (ie, without pancreatic parenchymal necrosis), whereas in the updated Atlanta Classification, peripancreatic necrosis is also included under necrotizing pancreatitis.<sup>25</sup> Second, most of the reviewed studies were performed at a time when the previously mentioned changes regarding intervention had not yet fully occurred. Third, most reviewed studies are small retrospective case series. Although there are some larger studies, with sample sizes ranging from 281 to 392 patients, these studies cover long periods (range, 12–19 years).<sup>26–28</sup> Fourth, because most studies report only the subgroup of patients who underwent operative necrosectomy,<sup>22,27,29,30</sup> data on the outcome of conservative treatment of necrotizing pancreatitis and outcome of emergency laparotomy are scarce. Fifth, although sterile necrosis should be managed conservatively, many of the reviewed studies report low proportions of infected necrosis (range, 63%–74%).<sup>22,29,30</sup> Sixth, whereas percutaneous drainage alone may be sufficient treatment in a proportion of patients, the percentage of patients undergoing percutaneous drainage before necrosectomy is low (range, 5%–30%) or not even reported.<sup>12,26,29–31</sup> Finally, the vast majority of data comes from highly experienced single

centers.<sup>12,26,27,29–31</sup> It is questionable whether these results can be extrapolated to daily practice in nonexpert centers. Given all these factors, new data from large prospective multicenter studies are needed to serve as a reference for the current outcome of necrotizing pancreatitis.

The aim of this study was to evaluate the outcome of conservative and interventional treatment in a prospective nationwide cohort of 639 patients covering the entire clinical spectrum of necrotizing pancreatitis in recent years. We also analyzed outcome in disease subgroups based on organ failure, pancreatic or peripancreatic necrosis, and status of infection.

## Patients and Methods

### *Patients and Study Design*

We performed a prospective observational cohort study between March 2004 and November 2008 in all 8 Dutch university medical centers and 13 large teaching hospitals of the Dutch Pancreatitis Study Group. The study aims, outcomes, definitions, and end points were predefined. During the study period, all patients admitted with acute pancreatitis were registered in a prospective database and were screened for eligibility for the PROPATRIA and PANTER randomized trials.<sup>24,32</sup> Regardless of eligibility for the trials, patients were included in the current prospective study if they met the inclusion criteria of signs of pancreatic necrosis and/or peripancreatic necrosis on contrast-enhanced computed tomography (CECT).<sup>33</sup> This is the first time this complete cohort is reported. The study was conducted in accordance with the principles of the Declaration of Helsinki. The ethics review board of each participating hospital approved the study. Patients or their legal representatives gave written informed consent. We adhered to the STROBE guidelines for reporting observational cohort studies.<sup>34</sup>

### *Computed Tomography*

CECT was performed per protocol in the patients randomized in the PROPATRIA study 7 to 10 days after admission and on demand thereafter and thereafter.<sup>32</sup> In all other patients, CECT was performed at the discretion of the treating physician but generally only in case there was no clinical improvement after the initial 7 to 10 days of admission. Local radiologists judged the CECT for pancreatic necrosis and/or peripancreatic necrosis, and based on their evaluation, patients were prospectively included. However, after the study was completed, all digitalized CECTs were reviewed by an experienced abdominal radiologist (T.L.B.) who was unaware of the clinical background and treatment. He made the final decision on inclusion or exclusion based on the highest computed tomography (CT) severity index<sup>33</sup> measured on all CECTs performed during admission. Median time between onset of symptoms and the final CECT before discharge was 14 days (interquartile range [IQR], 7–47).

### *Treatment Protocol*

The following treatment was protocolized. After admission, patients received rigorous fluid resuscitation, and full laboratory investigations were performed on the first 3 days and in the 24 hours before any intervention. Nasojejunal enteral feeding was initiated if an oral diet was not tolerated. Parenteral nutrition was only initiated when enteral nutrition was not tolerated or not sufficient. Half the patients randomized in the PROPATRIA trial received probiotic prophylaxis (n = 105).<sup>32</sup>

Antibiotics were administered only in the presence of suspected or documented infection. Patients with (pending) organ failure were treated in the intensive care unit.

In line with international guidelines, intervention was generally only performed in case of suspected or confirmed infection of pancreatic necrosis or peripancreatic necrosis alone.<sup>3,10,11</sup> There was no routine fine-needle aspiration of peripancreatic collections. The decision to intervene was mostly based on clinical grounds (ie, deterioration). Whenever possible, intervention was postponed until approximately 4 weeks after the onset of disease. In case of proven or suspected infection of pancreatic necrosis within 4 weeks after onset of disease, antibiotics were administered and intervention was postponed as long as possible.<sup>14-16</sup> Some patients underwent emergency laparotomy early in the course of disease. The indication was severe clinical deterioration suspected to be caused by abdominal compartment syndrome, bowel ischemia, or perforation of a visceral organ.

In early 2006, we installed a multidisciplinary expert panel consisting of 8 gastrointestinal surgeons, one gastroenterologist, and 3 radiologists to guide decisions on intervention. Whenever infected necrosis was suspected or there was any other indication for intervention, the expert panel received a case description, including CT images, on a standardized form by e-mail. Within 24 hours, the members of the expert panel individually advised on the indication for intervention and possible methods of interventions. The ultimate decision for intervention was made by the treating physician.

Intervention could be primary necrosectomy, primary percutaneous catheter drainage with 12F to 14F drains,<sup>18</sup> or endoscopic transluminal (gastric wall or duodenal wall) catheter drainage,<sup>21</sup> with or without subsequent necrosectomy. Necrosectomy consisted of open necrosectomy by laparotomy and continuous postoperative lavage<sup>17</sup> or minimally invasive necrosectomy: video-assisted retroperitoneal debridement (VARD)<sup>20</sup> or endoscopic transluminal necrosectomy (ETN).<sup>21</sup> A subgroup of patients included in the PANTER trial<sup>24</sup> was randomly assigned to either primary open necrosectomy (n = 45) or a protocolized step-up approach that included primary catheter drainage, followed, if necessary, by VARD (n = 43).

### Definitions

Pancreatic necrosis was defined as a CT severity index of >4, which means focal nonenhancement of the pancreatic gland. Peripancreatic necrosis alone (ie, without pancreatic parenchymal necrosis) was defined as a CT severity index of 3 or 4, which means peripancreatic morphologic changes exceeding fat stranding. In the most recent draft of the revised Atlanta Classification,<sup>25</sup> the definition of necrotizing pancreatitis includes both pancreatic parenchymal necrosis with or without peripancreatic necrosis and peripancreatic necrosis alone.

### Data Collection

Data from patients randomized in the PROPATRIA and PANTER trial were collected as described previously.<sup>24,32</sup> In addition, data from the other patients were entered prospectively into a database. This included data on patient demographics, laboratory investigations in the first 3 days of admission and 24 hours before intervention, clinical course, microbiology cultures, and interventions. If a patient had been referred from another center, all CECTs, clinical data, and laboratory investigations were retrieved.

**Table 1.** Definitions of Complications

Complication	Definition
Infected necrosis	A positive culture of pancreatic necrosis or peripancreatic necrosis obtained by means of fine-needle aspiration or from the first drainage procedure or necrosectomy, or the presence of gas in the peripancreatic collection on CECT
Organ failure	
Pulmonary failure	PaO <sub>2</sub> <60 mm Hg, despite FiO <sub>2</sub> of 0.30, or need for mechanical ventilation
Circulatory failure	Circulatory systolic blood pressure <90 mm Hg, despite adequate fluid resuscitation, or need for inotropic catecholamine support
Renal failure	Creatinine level >177 μmol/L after rehydration or new need for hemofiltration or hemodialysis
Multiple organ failure	Failure of at least 2 organ systems on the same day
Persistent organ failure	Presence of organ failure on at least 3 consecutive days (lasting more than 48 hours)
New-onset multiple organ failure	New-onset failure (ie, not present at any time in the 24 hours before first intervention) of 2 or more organs
Enterocutaneous fistula	Secretion of fecal material from a percutaneous drain or drainage canal after removal of drains or from a surgical wound, either from small or large bowel; confirmed by imaging or during surgery
Perforation of visceral organ	Perforation requiring surgical, radiologic, or endoscopic intervention
Intra-abdominal bleeding	Bleeding requiring surgical, radiologic, or endoscopic intervention

### Outcomes

The primary study outcome was mortality during index admission. Readmission within 10 days after discharge from index admission was considered a prolonged index admission. Secondary outcomes during admission were organ failure, infected necrosis, the number of drainage procedures, endoscopic and surgical necrosectomies, other operations, and complications (Table 1).

### Statistical Analysis

Analyses were performed with SPSS version 15.0 (Chicago, IL). The Kolmogorov-Smirnov test was used to assess whether continuous data were normally distributed ( $P > .05$ ). Continuous data are presented as mean ± SD and in case of nonnormal distributions as median with IQR. In case of missing data, patients were not included in the analyses for the specific parameter and this is reported. Differences were tested by the Mann-Whitney, Kruskal-Wallis, or linear-by-linear association tests for ordinal variables. Proportions were compared by the  $\chi^2$  test. When comparing different time points of intervention and methods of intervention (ie, drainage or necrosectomy), to reduce potential selection bias, we used multivariate logistic regression to adjust for prognostic baseline variables. These variables were age, CT severity index, American Society of Anesthesiologists (ASA) class, Acute Physiology And Chronic Health Evaluation II (APACHE II) score, and organ failure.

**Table 2.** Characteristics of 639 Patients With Necrotizing Pancreatitis

Characteristic	All patients (N = 639)	Conservative treatment (n = 397)	Intervention (n = 242)	P value
Age (y)	58 (45–70)	57 (43–71)	59 (48–69)	.41 <sup>a</sup>
Male sex (%)	398 (62)	237 (60)	161 (67)	.08 <sup>b</sup>
Etiology (%)				.41 <sup>b</sup>
Gallstones	304 (48)	192 (48)	112 (46)	
Alcohol abuse	150 (24)	95 (24)	55 (23)	
Other	63 (10)	42 (11)	21 (9)	
Unknown	122 (19)	68 (17)	54 (22)	
ASA class on admission (%)				.02 <sup>c</sup>
I (healthy status)	202 (32)	136 (34)	66 (27)	
II (mild systemic disease)	347 (54)	214 (54)	133 (55)	
III (severe systemic disease)	90 (14)	47 (12)	43 (18)	
Predicted severity of pancreatitis				
APACHE II score on admission	8 (5–11)	7 (5–10)	8 (5–11)	.25 <sup>a</sup>
APACHE II score >8 on admission (%)	324 (51)	192 (48)	132 (55)	.13 <sup>b</sup>
Imrie/modified Glasgow score (48 hours of admission)	3 (2–5)	3 (2–4)	4 (3–5)	<.001 <sup>a</sup>
Imrie/modified Glasgow score ≥3 (%)	413 (65)	225 (57)	188 (78)	<.001 <sup>b</sup>
Highest CRP level in first 48 hours of admission (mg/L)	291 (±130)	287 (±133)	294 (±129)	.51 <sup>a</sup>
CRP level >150 mg/L (%)	513 (80)	318 (80)	195 (81)	.42 <sup>b</sup>
No CRP data available (%)	44 (7)	32 (8)	12 (5)	
CT severity index	4 (4–8)	4 (4–6)	8 (6–10)	<.001 <sup>a</sup>
Pancreatic necrosis (%)	324 (51)	139 (35)	185 (76)	<.001 <sup>b</sup>
Peripancreatic necrosis alone (%)	315 (49)	258 (65)	57 (24)	<.001 <sup>b</sup>
Extent of pancreatic necrosis (%)				<.001 <sup>c</sup>
<30%	447 (70)	329 (83)	118 (49)	
30% to 50%	83 (13)	25 (6)	58 (24)	
>50%	109 (17)	43 (11)	66 (27)	
Transferred from other hospital (%)	156 (24)	39 (10)	117 (48)	<.001 <sup>b</sup>

NOTE. Continuous variables are mean (±SD) or median (IQR).

CRP, C-reactive protein. It was not possible to measure CRP in 1 hospital.

<sup>a</sup>Mann-Whitney test.

<sup>b</sup>χ<sup>2</sup> test.

<sup>c</sup>Linear-by-linear association.

Results of the adjusted analyses are presented as odds ratios with corresponding 95% confidence intervals. A 2-sided *P* value of <.05 was considered statistically significant.

## Results

During the 4.5-year study period, 639 patients with pancreatic necrosis or peripancreatic necrosis alone were included. No data were missing with regard to the primary and secondary study outcomes. Patient characteristics on admission and details from the CECTs before any intervention are given in Table 2. Overall mortality was 15% (93/639).

Table 3 lists mortality for the several treatment and disease subgroups that will be consecutively presented.

### Conservative Treatment

Conservative treatment (ie, without any radiologic, endoscopic, or surgical intervention) was performed in 397 of 639 patients (62%). Characteristics on admission for these patients are shown in Table 2. Overall mortality was 7% (28/397).

The group of 397 patients treated conservatively included 63 patients (16%) with organ failure and 11 patients (3%) with infected necrosis. The latter 11 patients were only treated with intravenous antibiotics because of

their extraordinary good clinical condition in the absence of sepsis or organ failure. Mortality in the patients with organ failure and conservative treatment was 37% (23/63), and mortality in the 11 patients with infected necrosis and conservative treatment was 0%.

### Interventional Treatment

An intervention was performed in 242 of 639 patients (38%). A flowchart of patients undergoing intervention is shown in Figure 1.

As compared with patients treated conservatively, patients undergoing intervention had higher ASA class, Imrie score, CT severity index, and extent of pancreatic necrosis on admission (Table 2). During admission, 177 of 242 patients (73%) developed organ failure and 189 of 242 patients (78%) developed infected necrosis. Mortality in patients undergoing intervention was 27% (65/242).

Table 4 shows the baseline criteria for patients undergoing intervention, subdivided in 3 time periods. The longer the time between admission and intervention, the lower the risk of mortality: 0 to 14 days, 56% (25/45); 14 to 29 days, 26% (25/98); and >29 days, 15% (15/99) (*P* < .001). This did not change when adjusted for baseline prognostic factors (age, APACHE II, CT severity index, organ failure, ASA class), with

**Table 3.** Mortality in the Different Subgroups of the 639 Patients With Necrotizing Pancreatitis

Subgroups	Mortality
All patients with necrotizing pancreatitis	93/639 (15)
Pancreatic necrosis	64/324 (20)
Peripancreatic necrosis alone	29/315 (9)
No organ failure	8/399 (2)
Organ failure	
At any time during admission	85/240 (35)
At any time during admission, persistent	77/213 (36)
In the first week of admission	57/140 (41)
Multiple organ failure	
At any time during admission	79/194 (41)
At any time during admission, persistent	66/161 (41)
In the first week of admission	44/94 (47)
Infected or sterile necrosis	
Primary infected necrosis	41/202 (20)
Sterile necrosis	52/437 (12)
Conservative treatment or intervention	
Conservative treatment	28/397 (7)
Any intervention (ie, emergency laparotomy, drainage, necrosectomy)	65/242 (27)
Emergency laparotomy	25/32 (78)
Any intervention for suspected or confirmed infected necrosis	40/208 (19)
Catheter drainage as first intervention	26/130 (20)
Necrosectomy as first intervention	14/78 (18)
Necrosectomy (with or without previous drainage or emergency laparotomy)	41/169 (24)
Any operation (ie, necrosectomy or emergency laparotomy)	56/187 (30)

NOTE. All values in parentheses are percentages.

an adjusted odds ratio of 0.38 and 95% confidence interval of 0.24 to 0.59 ( $P < .001$ ).

**Early emergency laparotomy.** An emergency laparotomy was necessary in 32 of 639 patients (5%) at a median of 5 days (IQR, 2–14) after admission. These laparotomies were not performed for suspected or confirmed infected necrosis but because of an abdominal catastrophe for another reason. There were signs of abdominal compartment syndrome in 15 patients, and bowel ischemia was observed during laparotomy in 11 patients. Of the 32 patients undergoing emergency laparotomy, 25 patients (78%) died.

**Interventions for infected necrosis.** A radiologic, endoscopic, or surgical intervention for suspected or confirmed infected necrosis was performed in 208 of 639 patients (33%). The cultures of the first intervention were positive in 89% (185/208). Details on disease severity at the time of intervention are given in Table 5. Median time between onset of symptoms and intervention was 28 days (IQR, 22–41). The first intervention was most often percutaneous (or endoscopic transluminal) catheter drainage (63%,  $n = 130$ ). Primary necrosectomy was performed in 78 of 208 patients (38%).

Half of the patients ( $n = 104$ ) undergoing intervention for infected necrosis experienced one or more complications. New-onset organ failure occurred in 83 of 208 patients (40%), intra-abdominal bleeding in 33 of 208 patients (16%), and enterocutaneous fistula or perforation

of a visceral organ in 35 of 208 patients (17%). The longer the time between admission and intervention, the lower the risk of complications: 0 to 14 days, 72% (13/18); 14 to 29 days, 57% (53/93); and >29 days, 39% (38/97) ( $P = .007$ ). This did not change when adjusted for baseline variables, with an adjusted odds ratio of 0.46 and 95% confidence interval of 0.29 to 0.73 ( $P = .001$ ).

In the 130 patients undergoing catheter drainage as first intervention (percutaneous,  $n = 113$ ; endoscopic transluminal,  $n = 17$ ), a median of 1 drainage procedure (IQR, 1–2) was performed per patient; 75 of 130 patients (58%) underwent 1 drainage procedure, 42 of 130 patients (32%) underwent 2 drainage procedures, and 13 of 130 patients (10%) had more than 2 drainage procedures. Forty-five of the 130 patients (35%) who underwent primary drainage were successfully treated without any necrosectomy and left the hospital in good clinical condition. Nine of 130 patients (7%) treated with primary catheter drainage died without undergoing any other intervention. These patients were not considered candidates for surgery due to poor clinical condition and comorbidity.

Following primary catheter drainage, after a median of 10 days (IQR, 5–22), 76 of 130 patients (58%) underwent additional necrosectomy (laparotomy,  $n = 25$ ; VARD,  $n = 44$ ; ETN,  $n = 7$ ). Mortality was 22% (17/76). There were no significant differences in mortality or the number of patients with complications for the different techniques of necrosectomy (data not shown).

Seventy-eight patients underwent necrosectomy as first intervention (laparotomy,  $n = 68$ ; VARD,  $n = 6$ ; or ETN,  $n = 4$ ). Mortality was 18% (14/78), and this did not differ significantly for the different techniques of necrosectomy (data not shown). The number of patients with complications was significantly greater in patients undergoing laparotomy as compared with VARD and ETN (71% [48/68] vs 33% [2/6] vs 0% [0/4], respectively;  $P = .004$ ).

Fewer complications occurred in patients undergoing catheter drainage as first intervention than in patients undergoing primary necrosectomy (42% [54/130] vs 64% [50/78], respectively;  $P = .003$ ; adjusted odds ratio, 0.37; 95% confidence interval, 0.19–0.67;  $P = .001$ ). This difference was mainly driven by a lower incidence of new-onset multiple organ failure after primary drainage (17% [22/130] vs 31% [24/78],  $P = .02$ ). There was no difference in mortality (20% [26/130] vs 18% [14/78],  $P = .71$ ).

### Disease Subgroups

**Organ failure.** Organ failure during admission occurred in 240 of 639 patients (38%). Mortality occurred almost exclusively in patients with organ failure as compared with patients without organ failure (35% [85/240] vs 2% [8/399],  $P < .001$ ).

The vast majority of patients with organ failure had persistent (>48 hours) organ failure (213/240; 89%). Mortality for patients with transient organ failure and persistent organ failure did, however, not differ significantly (30% [8/27] vs 36% [77/213],  $P = .51$ ).

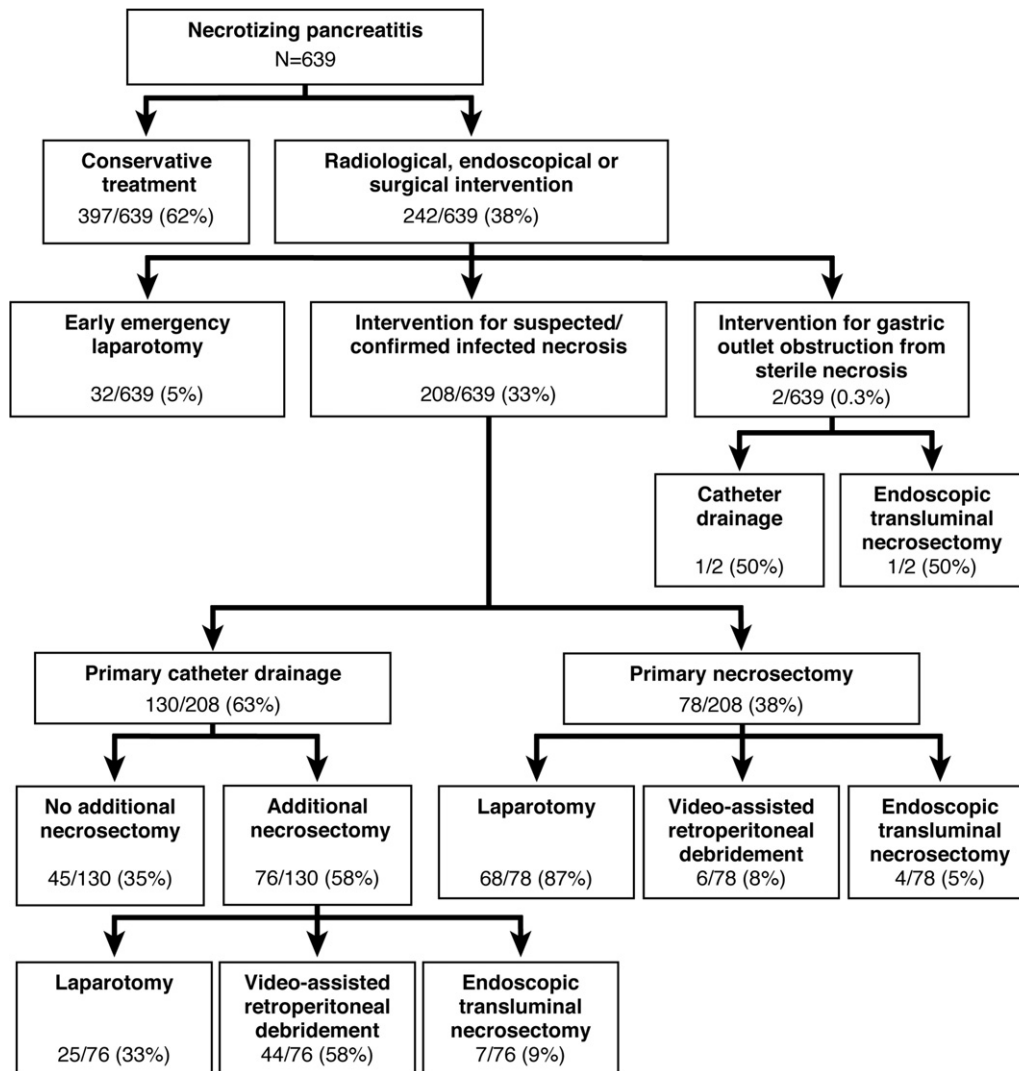


Figure 1. Flowchart on treatment strategies in 639 patients with necrotizing pancreatitis.

Multiple organ failure occurred in 194 of 639 patients (30%) and persistent multiple organ failure in 161 of 639 patients (25%). Mortality for transient and persistent multiple organ failure was 40% (13/33) and 41% (66/161), respectively ( $P = .87$ ).

More than half of the cases (140/240 [58%]) of organ failure occurred within the first week of admission. Mortality was higher in patients with organ failure in the first week of admission as compared with patients with organ failure after the first week of admission (41% [57/140] vs 28% [28/100],  $P = .04$ ). Multiple organ failure in the first week was associated with 47% (44/94) mortality.

**Type of necrosis.** On CECT, 324 of 639 patients (51%) had signs of pancreatic parenchymal necrosis and 315 of 639 patients (49%) had signs of peripancreatic necrosis alone. Organ failure occurred more often in patients with pancreatic necrosis as compared with patients with peripancreatic necrosis alone (50% [163/324] vs 24% [77/315],  $P < .001$ ). Mortality was also greater in patients with pancreatic necrosis than in patients with peripancreatic necrosis alone (20% [64/324] vs 9% [29/315],  $P < .001$ ).

**Infected necrosis.** Primary infection of necrosis was diagnosed in 202 of 639 patients (32%) at a median of 26 days (IQR, 18–38) after admission. The incidence of infected necrosis was higher in patients with pancreatic necrosis as compared with patients with peripancreatic necrosis alone (47% [151/324] vs 16% [51/315],  $P < .001$ ).

## Discussion

This is the largest prospective cohort of patients with necrotizing pancreatitis who underwent either conservative treatment or an intervention reported thus far. Compared with most of the earlier studies, this study included a large number of patients in a relatively short study period, was conducted in a nationwide multicenter setting, and covered the entire clinical spectrum of necrotizing pancreatitis. We showed that treatment can be conservative in about two-thirds of patients with necrotizing pancreatitis. In case of infected necrosis, one-third of patients can be successfully treated with percutaneous (or endoscopic transluminal) catheter drainage and do not need any form of

**Table 4.** Baseline Characteristics for Patients Who Underwent Early and Late Interventions

Characteristic	Time from admission to intervention (days)			P value
	0–14 (n = 45)	14–29 (n = 98)	More than 29 (n = 99)	
Age (y)	58 (±14)	58 (±13)	58 (±15)	.98 <sup>a</sup>
Male sex (%)	29 (64)	66 (67)	66 (67)	.94 <sup>b</sup>
Etiology (%)				.24 <sup>b</sup>
Gallstones	14 (31)	47 (48)	51 (52)	
Alcohol abuse	15 (33)	23 (24)	17 (17)	
Other	3 (7)	8 (8)	10 (10)	
Unknown	13 (29)	20 (20)	21 (21)	
ASA class on admission (%)				.71 <sup>c</sup>
I (healthy status)	11 (24)	26 (27)	29 (29)	
II (mild systemic disease)	26 (58)	55 (56)	52 (53)	
III (severe systemic disease)	8 (18)	17 (17)	18 (18)	
CT severity index	6 (5–10)	8 (4–8)	8 (6–10)	.76 <sup>a</sup>
Pancreatic necrosis (%)	35 (78)	70 (71)	80 (81)	.29 <sup>a</sup>
Peripancreatic necrosis alone (%)	10 (22)	28 (29)	19 (19)	.29 <sup>a</sup>
Extent of pancreatic necrosis (%)				.87 <sup>c</sup>
<30%	24 (53)	45 (46)	49 (50)	
30% to 50%	7 (16)	30 (31)	21 (21)	
>50%	14 (31)	23 (25)	29 (29)	
APACHE II at time of intervention	14 (10–21)	13 (9–19)	13 (8–17)	.14 <sup>a</sup>
Organ failure at time of intervention (%)	12 (27)	46 (47)	27 (27)	.006 <sup>b</sup>

NOTE. Continuous variables are mean (±SD) or median (IQR).

<sup>a</sup>Kruskal–Wallis test.

<sup>b</sup>χ<sup>2</sup> test.

<sup>c</sup>Linear-by-linear association

necrosectomy. If catheter drainage is unsuccessful, minimally invasive retroperitoneal and endoscopic transluminal necrosectomy are safe and feasible techniques.

We confirmed that approximately half of the patients with necrotizing pancreatitis who die have sterile necrosis. Mortality in these patients is almost exclusively caused by multiple organ failure in the first week.<sup>6,7</sup> There is currently no effective treatment to improve outcome in these patients. Intervention is generally contraindicated.<sup>3</sup> However, in 32 patients (5%) in the current study, an early emergency laparotomy was performed. As to be expected,

mortality was high (78%). Fifteen of these patients were suspected of having an abdominal compartment syndrome. There are only a few other studies on emergency laparotomy for abdominal compartment syndrome early in the course of acute pancreatitis.<sup>35–38</sup> These retrospective studies included 3 to 27 patients, with mortality varying from 30% to 75%. Interestingly, an 2007 international consensus conference suggested that catheter drainage of intra-abdominal fluid can be used as the initial step to decrease intra-abdominal pressure in patients with abdominal compartment syndrome in general.<sup>39</sup> This strategy may improve outcome and is currently being evaluated in acute pancreatitis ([ClinicalTrials.gov](http://ClinicalTrials.gov) NCT00793715).

Organ failure occurred in 38% of patients, with 35% mortality. This is in line with a recent meta-analysis of 14 cohorts of both interstitial and necrotizing pancreatitis, showing overall mortality after organ failure of 30%.<sup>40</sup> Several studies have suggested that early persisting organ failure rather than transient organ failure drives mortality in acute pancreatitis.<sup>5,6,41</sup> Interestingly, in the current study, the vast majority of patients with organ failure (89%) or multiple organ failure (83%) had persistent organ failure (ie, lasting for more than 48 hours). Mortality in patients with organ failure in the first week was significantly higher than in patients with organ failure occurring after the first week (41% vs 28%). This supports the theory that organ failure early in the course of acute pancreatitis, which is associated with systemic release of cytokines and systemic inflammatory response syndrome, is a different clinical entity than organ failure as a result of sepsis from infected necrosis at a later stage.

**Table 5.** Characteristics of 208 Patients Undergoing an Intervention for Infected Necrosis

Characteristic	Intervention for infected necrosis (n = 208)
APACHE II score <sup>a</sup>	13 (9–17)
C-reactive protein level <sup>a</sup>	200 (±109)
Admitted to the intensive care unit (%)	
At the time of intervention	75 (36)
Any time before intervention	140 (67)
Organ failure (%)	
At the time of intervention	76 (37)
Any time before intervention	113 (54)
Multiple organ failure (%)	
At the time of intervention	46 (22)
Any time before intervention	84 (40)
Infected necrosis confirmed by intraoperative culture (%)	185 (89)

NOTE. Continuous variables are mean (±SD) or median (IQR).

<sup>a</sup>Based on the maximal values 24 hours before intervention, C-reactive protein level was not available in 46 patients.

More than one-third of patients with necrotizing pancreatitis in our study underwent an intervention, which was associated with 27% mortality. Several guidelines<sup>3,9,15</sup> now advise to withhold intervention for several weeks after onset of symptoms, although there is only limited evidence for this from previous studies. A randomized study from 1997 suggested that delaying surgical intervention beyond the first 12 days, as compared with intervention as early as in the first 72 hours of admission, reduces mortality.<sup>13</sup> Two retrospective studies<sup>14,16</sup> and one systematic review<sup>16</sup> have suggested that postponing surgery for approximately 4 weeks after admission further improves outcome. The current study yields further evidence in favor of delaying intervention whenever possible, as we found that morbidity and mortality decreased considerably if intervention was postponed. Notably, this is the first time that improved outcome for delayed intervention is reported in an analysis adjusted for potential confounders regarding patient characteristics and disease severity (ie, age, ASA class, organ failure, APACHE II score, CT severity index).

Infection of necrosis occurred in approximately 30% of patients with necrotizing pancreatitis. This shows that the incidence of infected necrosis has remained fairly constant over the past 20 years.<sup>9</sup> Mortality in infected necrosis in our study was 20%. This seems to be lower than the mortality of approximately 30% for infected necrosis reported in reviews of the literature of the past 2 decades.<sup>9,40</sup> However, our results are difficult to compare with the literature because most published reports present only selected subgroups of patients with infected necrosis (eg, only those who underwent necrosectomy, excluding emergency laparotomy). Moreover, large, prospective, unselected cohort studies on infected necrosis are rare.<sup>42</sup> In the current cohort of 639 patients, 33% underwent an intervention for suspected or confirmed infected necrosis. Approximately one-third of patients with infected necrosis were successfully managed with catheter drainage only. A median of 1 drainage procedure with normal-sized drains (ie, 12F–14F) was sufficient. In these patients, decompression of the infected collection with fluid/pus seems to be enough for full recovery, meaning that major abdominal surgery is not necessary. Patients who were treated with the step-up approach, using drainage as primary intervention and only followed by minimally invasive necrosectomy if needed, also had fewer complications than patients undergoing primary necrosectomy. These results are in line with our recent multicenter PANTER trial.<sup>24</sup> We advise that all patients with suspected or confirmed infected necrosis are treated with percutaneous or endoscopic catheter drainage first.

In the patients undergoing primary necrosectomy, minimally invasive necrosectomy was associated with fewer complications. There are few other studies that have directly compared minimally invasive necrosectomy with open necrosectomy.<sup>22,43</sup> In a retrospective case-matched study in 30 patients, minimally invasive retroperitoneal necrosectomy was associated with a marked reduction in

postoperative multiple organ failure.<sup>43</sup> A recent retrospective single-center study compared 137 patients who underwent minimally invasive retroperitoneal necrosectomy with 52 patients who underwent open necrosectomy.<sup>22</sup> Complications and mortality were significantly lower after minimally invasive retroperitoneal necrosectomy than after open necrosectomy (55% vs 81% and 19% vs 38%, respectively). These studies confirm the hypothesis that minimally invasive necrosectomy induces less surgical stress (ie, a proinflammatory immune response) in these already critically ill patients. Next to minimally invasive surgical techniques, endoscopic necrosectomy through the stomach or duodenum is also gaining popularity.<sup>21,44,45</sup> The 2 largest and most recent case series have shown that ETN is safe and feasible and seems to compare favorably with the literature on surgical necrosectomy, with complication rates of approximately 14% to 49% and mortality of 6% to 7.5%.<sup>44,45</sup> In the current study, ETN was performed as primary intervention in 7 patients and was associated with no complications and no deaths. However, low patient numbers and possible selection bias may explain these favorable results. Results from the first randomized trial comparing ETN with surgical necrosectomy are awaited (PENGUIN trial; ISRCTN07091918).

Mortality in the subgroup of patients undergoing an intervention for suspected or confirmed infected necrosis in our study was 19%. This is comparable to the 24% mortality reported from Liverpool, England,<sup>22</sup> and the 15% mortality reported from Boston, both expert centers, in patients with infected necrosis.<sup>29</sup> In our study, 5% of patients with infected necrosis were successfully managed without any intervention. This has been previously reported in case reports and small case series.<sup>46–49</sup> Although our data confirm that a very small subset of patients with infected necrosis can be treated with antibiotics alone, infected necrosis should still be considered an indication for intervention in the overwhelming majority of patients. We recommend close monitoring of patients who have an extraordinarily good clinical condition that might justify conservative treatment.

Patients with pancreatic parenchymal necrosis had significantly higher mortality than patients with peripancreatic necrosis alone (20% vs 9%). There is only one other study that previously compared these 2 subgroups, and it showed similar mortality rates as our study.<sup>50</sup> Although the outcome of patients with parenchymal necrosis was substantially worse, patients with peripancreatic necrosis alone still had a considerable risk of organ failure (24%), infected necrosis (16%), and need for intervention (23%). The subgroup of patients in whom CECT shows normally enhancing pancreatic parenchyma but signs of peripancreatic necrosis should therefore also be monitored carefully.

This study has potential shortcomings. First, during the study period, CECT was performed in patients admitted with acute pancreatitis by discretion of the treating physician (with the exception of the 296 patients in the PROPATRIA study who underwent CECT per protocol). Hence, there may be a small group of patients in whom

CECT was not performed because either their clinical condition was exceptionally good or they were too ill to undergo CECT. These patients may have been missed for inclusion. Second, selection bias may have occurred for the comparative analyses on the different interventions and timing of intervention, because this study did not have a randomized design, even though our analyses adjusting for baseline prognostic factors did not confirm this. Third, we classified patients as having peripancreatic necrosis alone if the highest CT severity index<sup>33</sup> measured during admission was 3 or 4. One can argue that this definition is not 100% accurate, especially as it has been suggested that peripancreatic necrosis cannot be reliably diagnosed by CECT.<sup>51,52</sup> However, several studies showed a good correlation between peripancreatic findings on CECT and the presence of fat necrosis at operation or autopsy.<sup>53–55</sup> Moreover, the median time between onset of symptoms and the last CECT in our study was 14 days. If a patient shows a heterogeneous peripancreatic collection on CECT (ie, corresponding to a CT severity index of 3–4) 2 weeks into the disease, this should be considered fat necrosis until proven otherwise.<sup>54</sup> Notably, in all patients with signs of peripancreatic necrosis alone on CECT in whom necrosectomy was performed, peripancreatic fat necrosis was found during operation.

In conclusion, this large and prospective multicenter study showed that about two-thirds of patients with necrotizing pancreatitis can be treated conservatively with relatively low mortality. Early emergency laparotomy and multiple organ failure, however, remain associated with high mortality. Patients with infected necrosis benefit from postponing intervention and minimally invasive techniques. One-third of these patients can be treated with percutaneous (or endoscopic transluminal) catheter drainage only and do not require necrosectomy.

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The authors disclose no conflicts

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