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Improving the Treatment of Necrotizing Pancreatitis — A Step Up

Andrew L. Warshaw, M.D.

Acute pancreatitis in most patients is self-limited and resolves without complications or the need for invasive procedures or surgical intervention. In a minority of patients, perhaps 10%, necrosis of the pancreatic and peripancreatic tissues opens the door to multiple organ failure, infection of the necrotic tissue, or both, with a greatly increased risk of death; this risk has been estimated to be 20 to 30%. Recent reports citing a substantial reduction in the rate of death, ranging as low as 4%,[1,2] attribute the improvement to better intensive care; avoidance of early intervention to allow resuscitation, stabilization, and demarcation and liquefaction of the damaged areas[2,3]; and a variety of innovations in drainage and evacuation of fluid and devitalized tissues. The established techniques of laparotomy and open débridement[1,2,4] are being challenged by "minimally invasive" endoscopic necrosectomy through transgastric, laparoscopic, and retroperitoneal routes.[5] The goals in general are control of infection, maximal evacuation of devitalized tissues that are the culture medium for invasive infection, and promotion of conditions for healing.

The indications for surgical intervention certainly do not include the mere presence of asymptomatic necrosis, even if it is substantial.[6] Many clinicians argue that infection is the sine qua non,[7] but some patients with sterile necrosis nonetheless have a major systemic inflammatory response and multiple organ failure,[2,6] and these patients can benefit from débridement. Other patients have a low-grade inflammatory state or they are "persistently unwell" for months,[1,2] and as many as 40% of these patients may have unsuspected infection of the necrotic tissue.[2]

There is now a consensus that the best outcomes from intervention are achieved when débridement is delayed until approximately 4 weeks after the onset of pancreatitis, when the damaged area has been walled off and liquefaction has begun.[1-3] If necessary, acute sepsis can be preliminarily controlled by percutaneous drainage as a bridge to the later evacuation of detritus.[5,8] Although percutaneous drainage alone has been associated with some success in the treatment of pancreatic "abscesses," the success rate in definitively treating infected necrotic tissue without the need for débridement is only 30 to 35%.[8,9]

In this issue of the *Journal,* van Santvoort et al.[9] report the results of a randomized trial comparing treatment of pancreatic and peripancreatic necrosis by open laparotomy with a hybrid, or "step-up," approach in which percutaneous drainage was the first step, with débridement by means of a less invasive video-assisted retroperitoneal

débridement (VARD) route reserved for patients in whom the drainage failed. Participation by 19 institutions was required to accomplish the goals of the trial, and even so, only 88 of 378 patients with necrotizing pancreatitis and confirmed or suspected infection met the inclusion criteria, which included the feasibility of a retroperitoneal access route. A total of 81 of these 88 patients ultimately had proven infected necrotic tissue. Whenever possible, the intervention was not undertaken until approximately 4 weeks after the onset of pancreatitis.

The primary end point selected for the study was a composite of major complications (new-onset multiple organ failure, perforation of a viscus, enterocutaneous fistula, or hemorrhage) or death. With the use of this criterion, the primary end point occurred in only 40% of patients treated with the step-up approach, as compared with 69% of patients who underwent open necrosectomy (P=0.006). However, since the rate of death did not differ between the two groups, the benefits of the step-up strategy accrued from fewer complications (e.g., 5 of 43 patients in the step-up group vs. 19 of 45 patients in the open-necrosectomy group had new-onset organ failure).

Notably, 35% of patients in the step-up group required only the first step (percutaneous drainage), and they apparently tolerated any residual necrotic tissues without a need for débridement. The surprising aspect of this latter observation is that the necrotic tissues left behind must also have been infected, and it is generally assumed that infected necrosis must be removed — in truth, that is the underlying premise for this study. The authors hypothesize that evacuation of the infected fluid component by means of percutaneous aspiration suffices because the solid debris may be sterile, but it seems more likely that the concomitant antibiotic treatment may succeed in overcoming the residual infection in some patients, as has been anecdotally reported. Nonetheless, the challenges of adequate débridement were apparent in both groups: one third of each group required multiple attempts (53 attempts in 26 patients who underwent VARD and 91 attempts in 45 patients who underwent open necrosectomy). These figures are significantly higher than the reoperation rate (13%) reported in a recent U.S. study,[2] and the length of hospitalization — similar with both methods of treatment — averaged 55 days, which was substantially longer than the 26 to 38 days reported in North American studies.[1,2,10]

Part of this longer length of stay may be attributed to differences in clinical practice in the United States and in the Netherlands. However, both techniques included factors that added to the duration of treatment and its costs. Open necrosectomy involved a continuous high-volume lavage through catheters placed at laparotomy until the effluent no longer contained the products of necrosis — a period that could have lasted many weeks. With the step-up approach, there was frequently an interval of 6 days or longer (median, 10) between the decision to intervene and the first VARD, during which percutaneous aspiration was performed in two trials before failure was declared; all the patients who required VARD also underwent postprocedural lavage. These labor-intensive treatments also added considerably to the overall cost of the treatment and disproportionately biased the reported cost of the group treated by means of open laparotomy in this study.

Despite its limitations, this is an excellent study. The feasibility and probable greater safety of the step-up approach to necrotizing pancreatitis is an important synthesis and integration of evolving techniques. As such, it is a major contribution that is likely to change our practice, at least for a segment of patients with severe acute pancreatitis. However, its limitations include the narrow applicability of the step-up approach because of the need for a retroperitoneal access route, the need in both groups for multiple operative interventions, and an overall mortality of 17%, which is 50 to 100% higher than the rate of death reported in recent studies from North America.[1,2,10] In addition, as the authors note, this study addresses a comparison of percutaneous drainage plus VARD with open necrosectomy and does not address whether VARD is superior to open necrosectomy when necrosectomy is needed. The alternative treatment options for necrotizing pancreatitis still require both careful judgment and special skills.

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ORIGINAL ARTICLE

A Step-up Approach or Open Necrosectomy for Necrotizing Pancreatitis

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ABSTRACT

BACKGROUND

Necrotizing pancreatitis with infected necrotic tissue is associated with a high rate of complications and death. Standard treatment is open necrosectomy. The outcome may be improved by a minimally invasive step-up approach.

METHODS

In this multicenter study, we randomly assigned 88 patients with necrotizing pancreatitis and suspected or confirmed infected necrotic tissue to undergo primary open necrosectomy or a step-up approach to treatment. The step-up approach consisted of percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy. The primary end point was a composite of major complications (new-onset multiple-organ failure or multiple systemic complications, perforation of a visceral organ or enterocutaneous fistula, or bleeding) or death.

RESULTS

The primary end point occurred in 31 of 45 patients (69%) assigned to open necrosectomy and in 17 of 43 patients (40%) assigned to the step-up approach (risk ratio with the step-up approach, 0.57; 95% confidence interval, 0.38 to 0.87; P=0.006). Of the patients assigned to the step-up approach, 35% were treated with percutaneous drainage only. New-onset multiple-organ failure occurred less often in patients assigned to the step-up approach than in those assigned to open necrosectomy (12% vs. 40%, P=0.002). The rate of death did not differ significantly between groups (19% vs. 16%, P=0.70). Patients assigned to the step-up approach had a lower rate of incisional hernias (7% vs. 24%, P=0.03) and new-onset diabetes (16% vs. 38%, P=0.02).

CONCLUSIONS

A minimally invasive step-up approach, as compared with open necrosectomy, reduced the rate of the composite end point of major complications or death among patients with necrotizing pancreatitis and infected necrotic tissue. (Current Controlled Trials number, ISRCTN13975868.)

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ACUTE PANCREATITIS IS THE THIRD MOST common gastrointestinal disorder requiring hospitalization in the United States, with annual costs exceeding $2 billion.[1,2] Necrotizing pancreatitis, which is associated with an 8 to 39% rate of death, develops in approximately 20% of patients.[3] The major cause of death, next to early organ failure, is secondary infection of pancreatic or peripancreatic necrotic tissue, leading to sepsis and multiple organ failure.[4] Secondary infection of necrotic tissue in patients with necrotizing pancreatitis is virtually always an indication for intervention.[3,5-7]

The traditional approach to the treatment of necrotizing pancreatitis with secondary infection of necrotic tissue is open necrosectomy to completely remove the infected necrotic tissue.[8,9] This invasive approach is associated with high rates of complications (34 to 95%) and death (11 to 39%) and with a risk of long-term pancreatic insufficiency.[10-16] As an alternative to open necrosectomy, less invasive techniques, including percutaneous drainage,[17,18] endoscopic (transgastric) drainage,[19] and minimally invasive retroperitoneal necrosectomy, are increasingly being used.[14,20-22] These techniques can be performed in a so-called step-up approach.[23] As compared with open necrosectomy, the step-up approach aims at control of the source of infection, rather than complete removal of the infected necrotic tissue. The first step is percutaneous or endoscopic drainage of the collection of infected fluid to mitigate sepsis; this step may postpone or even obviate surgical necrosectomy.[17-19] If drainage does not lead to clinical improvement, the next step is minimally invasive retroperitoneal necrosectomy.[14,20-22] The step-up approach may reduce the rates of complications and death by minimizing surgical trauma (i.e., tissue damage and a systemic proinflammatory response) in already critically ill patients.[14,21]

It remains uncertain which intervention in these patients is optimal in terms of clinical outcomes, health care resource utilization, and costs. We performed a nationwide randomized trial called Minimally Invasive Step Up Approach versus Maximal Necrosectomy in Patients with Acute Necrotising Pancreatitis (PANTER).

METHODS

STUDY DESIGN

The design and rationale of the PANTER study have been described previously.[24] Adults with acute pancreatitis and signs of pancreatic necrosis, peripancreatic necrosis, or both, as detected on contrast-enhanced computed tomography (CT), were enrolled in 7 university medical centers and 12 large teaching hospitals of the Dutch Pancreatitis Study Group. Patients with confirmed or suspected infected pancreatic or peripancreatic necrosis were eligible for randomization once a decision to perform a surgical intervention had been made and percutaneous or endoscopic drainage of the fluid collection was deemed possible.

Infected necrotic tissue was defined as a positive culture of pancreatic or peripancreatic necrotic tissue obtained by means of fine-needle aspiration or from the first drainage procedure or operation, or the presence of gas in the fluid collection on contrast-enhanced CT. Suspected infected necrosis was defined as persistent sepsis or progressive clinical deterioration despite maximal support in the intensive care unit (ICU), without documentation of infected necrosis.

The exclusion criteria were a flare-up of chronic pancreatitis, previous exploratory laparotomy during the current episode of pancreatitis, previous drainage or surgery for confirmed or suspected infected necrosis, pancreatitis caused by abdominal surgery, and an acute intraabdominal event (e.g., perforation of a visceral organ, bleeding, or the abdominal compartment syndrome).

Patients were randomly assigned to either primary open necrosectomy or the minimally invasive step-up approach. Randomization was performed centrally by the study coordinator. Permuted-block randomization was used with a concealed block size of four. Randomization was stratified according to the treatment center and the access route that could be used for drainage (i.e., a retroperitoneal route or only a transabdominal or endoscopic transgastric route).

STUDY OVERSIGHT

All patients or their legal representatives provided written informed consent before randomization. This investigator-initiated study was conducted in accordance with the principles of the Declaration of Helsinki. The institutional review board of each participating hospital approved the protocol.

QUALITY CONTROL

The indication for intervention and the optimal timing of intervention in necrotizing pancreatitis are frequently subject to discussion.[25] Therefore, an expert panel consisting of eight gastrointesti-

nal surgeons, one gastroenterologist, and three radiologists was formed. Whenever infected necrosis was suspected or there was any other indication for intervention in a patient, 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 assessed the indication for intervention and the patient's eligibility for randomization.

Whenever possible, the randomization and intervention were postponed until approximately 4 weeks after the onset of disease.[5,6,26,27] All interventions were performed by gastrointestinal surgeons who were experienced in pancreatic surgery and by experienced interventional radiologists and endoscopists. Whenever necessary, the most experienced study clinicians visited the participating centers to assist with interventions.

OPEN NECROSECTOMY

The open necrosectomy, originally described by Beger et al.,[8] consisted of a laparotomy through a bilateral subcostal incision. After blunt removal of all necrotic tissue, two large-bore drains for postoperative lavage were inserted, and the abdomen was closed.

MINIMALLY INVASIVE STEP-UP APPROACH

The first step was percutaneous or endoscopic transgastric drainage. The preferred route was through the left retroperitoneum, thereby facilitating minimally invasive retroperitoneal necrosectomy at a later stage, if necessary. If there was no clinical improvement (according to prespecified criteria[24]) after 72 hours and if the position of the drain (or drains) was inadequate or other fluid collections could be drained, a second drainage procedure was performed. If this was not possible, or if there was no clinical improvement after an additional 72 hours, the second step, video-assisted retroperitoneal débridement (VARD) with postoperative lavage,[21,22] was performed. (Details on the step-up approach and postoperative management in both groups are included in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

END POINTS AND DATA COLLECTION

The predefined primary end point was a composite of major complications (i.e., new-onset multiple organ failure or systemic complications, enterocutaneous fistula or perforation of a visceral organ requiring intervention, or intraabdominal bleeding requiring intervention) (Table 1) or death during admission or during the 3 months after discharge. The individual components of the primary end point were analyzed as secondary end points. Secondary end points also included other complications (Table 1), health care resource utilization, and total direct medical costs and indirect costs from admission until 6 months after discharge (details are available in the Supplementary Appendix).

Follow-up visits took place 3 and 6 months after discharge. Data collection was performed by local physicians using Internet-based case-record forms. An independent auditor who was unaware of the treatment assignments checked all completed case-record forms against on-site source data. Discrepancies detected by the auditor were resolved on the basis of a consensus by two investigators who were unaware of the study-group assignments and were not involved in patient care. All CT scans were prospectively evaluated by one experienced radiologist who was unaware of the treatment assignments and outcomes.

A blinded outcome assessment was performed by an adjudication committee consisting of eight experienced gastrointestinal surgeons who independently reviewed all data regarding complications. Disagreements were resolved during a plenary consensus meeting with concealment of the treatment assignments.

STATISTICAL ANALYSIS

We calculated that we would need to enroll 88 patients[24] in order to detect a 64% relative reduction in the rate of the composite primary end point with the step-up approach (from 45% to 16%), with a power of 80% and a two-sided alpha level of 0.05. The large risk reduction with the step-up approach was expected on the basis of results from a Dutch nationwide retrospective multicenter study[30] and other previous studies.[17,31] Moreover, a larger sample was not thought to be feasible because necrotizing pancreatitis with secondary infection is uncommon.
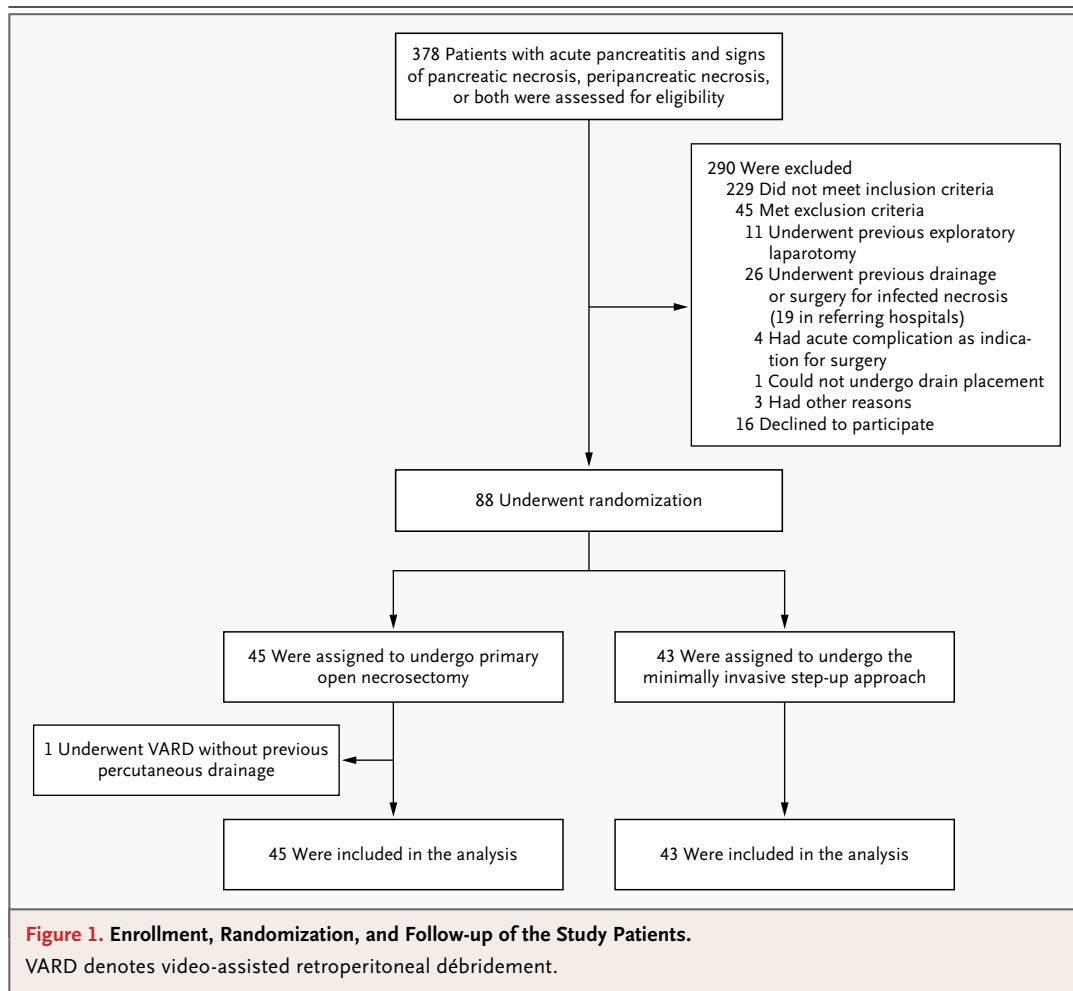
All analyses were performed according to the intention-to-treat principle. The occurrences of the primary and secondary end points were compared between the treatment groups. Results are presented as risk ratios with corresponding 95% confidence intervals. Differences in other outcomes were assessed with the use of the Mann–Whitney U test.

Predefined subgroup analyses were performed for the presence or absence of organ failure at

Table 1. Definitions of the Primary and Secondary End Points.*

End Point	Definition	Comment
Major complication		
New-onset multiple-organ failure or systemic complications	New-onset failure (i.e., not present at any time in the 24 hr before first intervention) of two or more organs or occurrence of two or more systemic complications at the same time	
Organ failure		Adapted from Bradley[28]
Pulmonary failure	PaO_2 <60 mm Hg, despite FIO_2 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/liter after rehydration or new need for hemofiltration or hemodialysis	
Systemic complication		Adapted from Bradley[28]
Disseminated intravascular coagulation	Platelet count <100×10^9/liter	
Severe metabolic disturbance	Calcium level <1.87 mmol/liter	
Gastrointestinal bleeding	>500 ml of blood/24 hr	
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	Before any analysis, the adjudication committee decided to combine the end points of enterocutaneous fistula and perforation of a visceral organ because one is often caused by the other and they may occur in the same patient
Perforation of visceral organ	Perforation requiring surgical, radiologic, or endoscopic intervention	Before any analysis, the adjudication committee decided to combine the end points of enterocutaneous fistula and perforation of a visceral organ because one is often caused by the other and they may occur in the same patient
Intraabdominal bleeding	Requiring surgical, radiologic, or endoscopic intervention	
Other outcome		
Pancreatic fistula	Output, through a percutaneous drain or drainage canal after removal of drains or from a surgical wound, of any measurable volume of fluid with an amylase content >3 times the serum amylase level	Adapted from Bassi et al.[29]
New-onset diabetes	Insulin or oral antidiabetic drugs required 6 mo after discharge; this requirement was not present before onset of pancreatitis	
Use of pancreatic enzymes	Oral pancreatic-enzyme supplementation required to treat clinical symptoms of steatorrhea 6 mo after discharge; this requirement was not present before onset of pancreatitis	
Incisional hernia	Full-thickness discontinuity in abdominal wall and bulging of abdominal contents, with or without obstruction, 6 mo after discharge	The original study protocol[24] stated "incisional hernia requiring intervention"; before any analysis, the adjudication committee decided to report incisional hernias with or without intervention because surgical reconstruction of the abdominal wall is usually not performed within 6 mo after recovery from necrotizing pancreatitis

* FIO_2 denotes fraction of inspired oxygen, and PaO_2 partial pressure of arterial oxygen.

Figure 1. Enrollment, Randomization, and Follow-up of the Study Patients.

VARD denotes video-assisted retroperitoneal débridement.

randomization and the timing of intervention (≤28 days or >28 days after the onset of symptoms). A formal test of interaction in a logistic-regression model was used to assess whether treatment effects differed significantly between the subgroups.

No interim analysis was performed. As a precautionary measure, an independent biostatistician who was unaware of the study-group assignments performed sequential monitoring[32] of the major complications and deaths reported during the trial (details are available in the Supplementary Appendix).

All reported P values are two-sided and have not been adjusted for multiple testing.

RESULTS

STUDY PARTICIPANTS

Between November 3, 2005, and October 29, 2008, a total of 378 patients with acute pancreatitis who had signs of pancreatic necrosis, peripancreatic necrosis, or both were enrolled in the study. A total of 88 patients were randomly assigned to a treatment group (Fig. 1). Baseline characteristics of the treatment groups were similar (Table 2).

PRIMARY OPEN NECROSECTOMY

Of the 45 patients assigned to primary open necrosectomy, 44 underwent a primary laparotomy. In one patient, who had previously undergone esophagectomy, it was decided after randomization that laparotomy would potentially compromise the gastric conduit. Therefore, primary VARD without previous percutaneous drainage was performed.

Patients underwent a median of 1 open necrosectomy (range, 1 to 7). Nineteen patients (42%) required one or more additional laparotomies for additional necrosectomy because of ongoing sepsis (in eight patients), complications (in five patients) or both (in six patients). Fifteen patients

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(33%) required additional percutaneous drainage after laparotomy.

MINIMALLY INVASIVE STEP-UP APPROACH

Forty of 43 patients assigned to the step-up approach (93%) underwent retroperitoneal percutaneous drainage; 1 patient (2%) underwent trans-

abdominal percutaneous drainage and 2 patients (5%) underwent endoscopic transgastric drainage. After the first 72 hours of observation, 19 patients (44%) underwent a second drainage procedure. Details of the drainage procedures are available in the Supplementary Appendix.

Fifteen patients (35%) survived after percuta-

Table 2. Baseline Characteristics of the Patients.*			
Characteristic	Minimally Invasive Step-up Approach (N=43)	Primary Open Necrosectomy (N=45)	P Value
Age — yr	57.6±2.1	57.4±2.0	0.94
Male sex — no. (%)	31 (72)	33 (73)	0.89
Cause of pancreatitis — no. (%)			0.98
Gallstones	26 (60)	29 (64)	
Alcohol abuse	3 (7)	5 (11)	
Other	14 (33)	11 (24)	
Coexisting condition — no. (%)			
Cardiovascular disease	19 (44)	21 (47)	0.82
Pulmonary disease	4 (9)	4 (9)	0.95
Chronic renal insufficiency	3 (7)	2 (4)	0.61
Diabetes	5 (12)	4 (9)	0.67
ASA class on admission — no. (%)			0.99
I: healthy status	11 (26)	11 (24)	
II: mild systemic disease	19 (44)	20 (44)	
III: severe systemic disease	13 (30)	14 (31)	
Body-mass index on admission†			0.12
Median	28	27	
Range	20–55	22–39	
CT severity index‡			0.95
Median	8	8	
Range	4–10	4–10	
Extent of pancreatic necrosis — no. (%)			0.52
<30%	17 (40)	19 (42)	
30% to 50%	14 (33)	10 (22)	
>50%	12 (28)	16 (36)	
Necrosis extending >5 cm down the paracolic gutter — no. (%)	24 (56)	27 (60)	0.69
Retroperitoneal access route to necrosis possible — no. (%)	40 (93)	40 (89)	0.50
Disease severity — no. (%)§			
SIRS¶	42 (98)	45 (100)	0.49
Admitted to ICU at time of randomization	23 (54)	21 (47)	0.52
Admitted to ICU at any time before randomization	28 (65)	29 (64)	0.95
Single-organ failure	21 (49)	22 (49)	0.99
Multiple-organ failure	15 (35)	13 (29)	0.55
Positive blood culture within previous 7 days	14 (33)	15 (33)	0.94
Positive blood culture at any time before randomization	22 (51)	25 (56)	0.68

Table 2. (Continued.)

Characteristic	Minimally Invasive Step-up Approach (N = 43)	Primary Open Necrosectomy (N = 45)	P Value
APACHE II score‖	14.6±6.1	15.0±5.3	0.75
APACHE II score ≥20 — no. (%)	10 (23)	9 (20)	0.71
MODS**			0.71
Median	2	1	
Range	0–9	0–10	
SOFA score‡‡			0.39
Median	3	2	
Range	0–11	0–12	
C-reactive protein — mg/liter	213.6±106	215.9±111	0.93
White-cell count — ×10⁻⁹/liter	17.6±10.6	15.9±6.3	0.38
Time since onset of symptoms — days			0.86
Median	30	29	
Range	11–71	12–155	
Antibiotic treatment at any time before randomization — no. (%)	37 (86)	38 (84)	0.83
Nutritional support at any time before randomization — no. (%)			0.92
Enteral feeding only	23 (54)	23 (51)	
Parenteral feeding only	3 (7)	4 (9)	
Enteral and parenteral feeding	12 (28)	11 (24)	
Oral diet	5 (12)	7 (16)	
Tertiary referral — no. (%)	21 (49)	23 (51)	0.83
Confirmed infected necrotic tissue — no. (%)§§	39 (91)	42 (93)	0.65

*   Plus–minus values are means ±SD. ASA denotes American Society of Anesthesiologists, CT computed tomography, and ICU intensive care unit.

†   The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡   Data were derived from the CT performed just before randomization. Scores on the CT severity index range from 0 to 10, with higher scores indicating more extensive pancreatic necrosis and peripancreatic fluid collections.

§   Data were based on maximum values during the 24 hours before randomization unless stated otherwise.

¶   The systemic inflammatory response syndrome (SIRS) was defined according to the consensus-conference criteria of the American College of Chest Physicians and the Society of Critical Care Medicine.

‖   Scores on the Acute Physiologic and Chronic Health Evaluation II (APACHE II) scale range from 0 to 71, with higher scores indicating more severe disease.

**   The Multiple Organ Dysfunction Score (MODS) ranges from 0 to 24, with higher scores indicating more severe organ dysfunction.

‡‡   Scores on the Sequential Organ Failure Assessment (SOFA) scale range from 0 to 24, with higher scores indicating more severe organ dysfunction.

§§   Infected necrotic tissue was defined as a positive culture of pancreatic or peripancreatic necrotic tissue obtained by means of fine-needle aspiration or from the first drainage procedure or operation, or the presence of gas in the fluid collection on contrast-enhanced CT.

neous or endoscopic drainage only, without the need for necrosectomy. The condition of two patients with progressive multiple organ failure was too unstable for surgery, and they subsequently died. The remaining 26 patients (60%) underwent necrosectomy a median of 10 days (range, 1 to 52) after percutaneous drainage. A VARD procedure was performed in 24 of the patients, and the other 2 patients underwent primary laparotomy according to the protocol because there was no retroperitoneal access route. A median of 1 VARD procedure (range, 0 to 3) was performed in each patient. In one patient, VARD was intraoperatively converted to laparotomy because it was not possible to reach the pancreatic necrosis through the retroperitoneum.

Fourteen patients (33%) required one or more additional operations for further necrosectomy

(five patients), complications (seven patients), or both (two patients). Seven of the 26 patients who underwent necrosectomy (27%) required percutaneous drainage afterward.

CLINICAL END POINTS

The primary and secondary end points are listed in Table 3. The composite primary end point of major complications or death occurred in 31 of 45 patients after primary open necrosectomy (69%) and in 17 of 43 patients after the step-up approach (40%) (risk ratio with the step-up approach, 0.57; 95% confidence interval [CI], 0.38 to 0.87; P=0.006). All major complications tended to occur more frequently after primary open necrosectomy than after the step-up approach, although the difference was significant only for the composite end point of new-onset multiple organ failure or multiple systemic complications (P=0.001). This difference was mainly driven by the occurrence of organ failure (Table 3).

The rate of death between the two study groups did not differ significantly (P=0.70) (Table 3). A total of 15 patients in the study died (17%): 8 patients in the step-up group (19%) and 7 patients in the open-necrosectomy group (16%). The causes of death were multiple organ failure in seven patients in the step-up group and six patients in the open-necrosectomy group, postoperative bleeding in one patient in the step-up group and no patients in the open-necrosectomy group, and respiratory failure due to pneumonia in no patients in the step-up group and one patient in the open-necrosectomy group.

At the 6-month follow-up, patients who had undergone primary open necrosectomy, as compared with patients who had been treated with the step-up approach, had a higher rate of incisional hernias (24% vs. 7%, P=0.03), new-onset diabetes (38% vs. 16%, P=0.02), and use of pancreatic enzymes (33% vs. 7%, P=0.002).

HEALTH CARE RESOURCE UTILIZATION AND COSTS

Utilization of health care resources for operations (i.e., necrosectomies and reinterventions for complications) was lower in the group of patients who were treated with the step-up approach than in the group of patients who underwent primary open necrosectomy (P=0.004) (Table 3). After primary open necrosectomy, 40% of patients required a new ICU admission, as compared with 16% of patients who had been treated with the step-up approach (P=0.01).

The mean total of direct medical costs and indirect costs per patient during admission and at the 6-month follow-up was €78,775 ($116,016) for the step-up approach and €89,614 ($131,979) for open necrosectomy, for a mean absolute difference of €10,839 ($15,963) per patient. Thus, the step-up approach reduced costs by 12% (details of costs are available in the Table in the Supplementary Appendix).

PREDEFINED SUBGROUP ANALYSES

Treatment effects with respect to the primary end point were similar across the subgroups on the basis of organ failure at the time of randomization and the timing of intervention (≤28 days or >28 days after the onset of symptoms). None of the tests for interaction were significant (P>0.05).

DISCUSSION

This study showed that the minimally invasive step-up approach, as compared with primary open necrosectomy, reduced the rate of the composite end point of major complications or death, as well as long-term complications, health care resource utilization, and total costs, among patients who had necrotizing pancreatitis and confirmed or suspected secondary infection. With the step-up approach, more than one third of patients were successfully treated with percutaneous drainage and did not require major abdominal surgery.

There are several possible explanations for the favorable outcome of the step-up approach. First, as we postulated when designing the study,[24] infected necrosis may be similar to an abscess because both contain infected fluid (pus) under pressure. Although a true abscess is more easily resolved with percutaneous drainage because it is composed entirely of liquid, simple drainage may also be sufficient to treat infected necrotic tissue. After the infected fluid is drained, the pancreatic necrosis can be left in situ, an approach that is similar to the treatment of necrotizing pancreatitis without infection. This hypothesis apparently holds true, since 35% of our patients who were treated with the step-up approach did not require necrosectomy.

Second, it has been suggested that minimally invasive techniques provoke less surgical trauma

Table 3. Primary and Secondary End Points.*

Outcome	Minimally Invasive Step-up Approach (N=43)	Primary Open Necrosectomy (N=45)	Risk Ratio (95% CI)	P Value
Primary composite end point: major complications or death — no. (%)†	17 (40)	31 (69)	0.57 (0.38–0.87)	0.006
Secondary end points				
Major complication — no. (%)				
New-onset multiple-organ failure or systemic complications‡	5 (12)	19 (42)	0.28 (0.11–0.67)	0.001
Multiple-organ failure	5 (12)	18 (40)		
Multiple systemic complications	0	1 (2)		
Intraabdominal bleeding requiring intervention	7 (16)	10 (22)	0.73 (0.31–1.75)	0.48
Enterocutaneous fistula or perforation of a visceral organ requiring intervention	6 (14)	10 (22)	0.63 (0.25–1.58)	0.32
Death — no. (%)	8 (19)	7 (16)	1.20 (0.48–3.01)	0.70
Other outcome — no. (%)				
Pancreatic fistula	12 (28)	17 (38)	0.74 (0.40–1.36)	0.33
Incisional hernia§	3 (7)	11 (24)	0.29 (0.09–0.95)	0.03
New-onset diabetes§	7 (16)	17 (38)	0.43 (0.20–0.94)	0.02
Use of pancreatic enzymes§	3 (7)	15 (33)	0.21 (0.07–0.67)	0.002
Health care resource utilization				
Necrosectomies (laparotomy or VARD) — no. (%)				<0.001
0	17 (40)	0		
1	19 (44)	31 (69)		
2	6 (14)	8 (18)		
≥3	1 (2)	6 (13)		
Total no. of operations¶				0.004
Per study group	53	91		
Range per patient	0–6	1–7		
Total no. of drainage procedures‖				<0.001
Per study group	82	32		
Range per patient	1–7	0–6		
New ICU admission at any time after first intervention — no. (%)**	7 (16)	18 (40)	0.41 (0.19–0.88)	0.01
Days in ICU				0.26
Median	9	11		
Range	0–281	0–111		
Days in hospital				0.53
Median	50	60		
Range	1–287	1–247		

* ICU denotes intensive care unit, and VARD video-assisted retroperitoneal débridement.
† Multiple events in the same patient were considered as one end point.
‡ This category included only patients without multiple-organ failure or multiple systemic complications at any time in the 24 hours before the first intervention.
§ Patients were assessed 6 months after discharge from the index admission (readmission within 10 days was considered the same admission).
¶ This category included necrosectomies (laparotomy or VARD procedure) and additional operations to treat complications (e.g., repeated laparotomy for abdominal bleeding) during the index admission.
‖ This category included primary drainage procedures as part of the minimally invasive step-up approach and additional drainage procedures after necrosectomy in both treatment groups during the index admission.
** This category included only patients who were not admitted to the ICU at any time in the 24 hours before the first intervention.

(i.e., tissue injury and a proinflammatory response) in patients who are already severely ill.[14,20,21] This hypothesis is supported by the substantial reduction in the incidence of new-onset multiple organ failure in our step-up group. Third, in the attempt to completely débride necrosis, viable pancreatic parenchyma may be unintentionally removed. This could explain why, at the 6-month follow-up, significantly more patients who underwent primary open necrosectomy had new-onset diabetes or were taking pancreatic enzymes. For pragmatic reasons, we defined pancreatic insufficiency on the basis of the use of pancreatic-enzyme supplements to treat clinical symptoms of pancreatic insufficiency instead of objective analyses of exocrine insufficiency (e.g., the fecal elastase test). It is possible that some of these patients did not have exocrine insufficiency, although the rate of pancreatic-enzyme supplementation in the open-necrosectomy group is consistent with data on exocrine insufficiency after open necrosectomy.[15]

Our findings are consistent with observations from several retrospective studies. It has been suggested previously that percutaneous drainage can be performed in almost every patient who has necrotizing pancreatitis with infection and obviates the need for necrosectomy in approximately half the patients.[17,18,33] Several authors have reported promising results of minimally invasive necrosectomy,[14,20,22] including endoscopic procedures.[19,34-36] Most studies, however, included only a small number of patients and may have unintentionally selected patients who were less ill than the patients treated with open necrosectomy or were better candidates for minimally invasive techniques. In contrast, the current study was randomized and included a relatively large number of patients, with a high incidence of confirmed infected necrotic tissue and organ failure at the time of intervention.

The benefit of the step-up approach in terms of preventing major abdominal surgery and associated complications, such as multiple organ failure requiring ICU admission, is of obvious importance. The reduction in long-term complications, including new-onset diabetes and incisional hernias, is also clinically relevant. Diabetes due to necrotizing pancreatitis is known to worsen over time.[15] Moreover, secondary complications from diabetes have a considerable effect on the quality of life and potentially on life expectancy. Incisional hernias often cause disabling discomfort

and pain, carry a risk of small-bowel strangulation, and frequently require surgical intervention.[37] Aside from these clinical implications, the estimated economic benefit from reduced health care resource utilization and costs may be substantial. Approximately 233,000 patients are admitted with a new diagnosis of acute pancreatitis in the United States each year,[38] and necrotizing pancreatitis with secondary infection develops in about 5% of these patients.[3,28] On the basis of these numbers, the step-up approach may reduce annual costs in the United States by $185 million.

The nationwide multicenter setting of our study and the applicability of the minimally invasive techniques provide support for the generalizability of its results. Percutaneous catheter drainage is a relatively easy and well-established radiologic procedure. VARD is considered a fairly straightforward procedure that can be performed by any gastrointestinal surgeon with basic laparoscopic skills and experience in pancreatic necrosectomy.[21,22]

Our study specifically compared two treatment strategies and does not provide a direct comparison of open necrosectomy with minimally invasive retroperitoneal necrosectomy. Although there are theoretical advantages of a minimally invasive approach, we have not proved that VARD is superior to open necrosectomy in patients in whom percutaneous drainage has failed.

This study was not designed or powered to demonstrate a difference in the rate of death between the two treatment strategies. A study showing a clinically relevant difference in mortality would require thousands of patients and is not likely to be performed.

Our results indicate that the preferred treatment strategy for patients with necrotizing pancreatitis and secondary infection, from both a clinical and an economic point of view, is a minimally invasive step-up approach consisting of percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy.

APPENDIX

The following investigators participated in the study: **Steering committee:** M.G. Besselink, M.A. Boermeester, T.L. Bollen, E. Buskens, C.H. Dejong, C.H. van Eijck, H. van Goor, H.G. Gooszen (chair), H.S. Hofker, J.S. Laméris, M.S. van Leeuwen, V.B. Nieuwenhuijs, R.J. Ploeg, B. van Ramshorst, H.C. van Santvoort, A.F. Schaapherder. **Expert panel:** M.A. Boermeester, T.L. Bollen, C.H. Dejong, C.H. van Eijck, H. van Goor, H.G. Gooszen, H.S. Hofker, J.S. Laméris, M.S. van Leeuwen, A.F. Schaapherder, R. Timmer, V.B. Nieuwenhuijs. **Independent data and safety monitoring committee:** F.L. Moll (chair), K.G. Moons, M. Prokop, M. Samsom, P.B. Soeters. **Independent biostatistician:** I. vd Tweel. **Independent data auditor:** J. Oors. **Adjudication committee:** M.A. Boermeester, C.H. Dejong, C.H. van Eijck, H. van Goor, H.G. Gooszen, H.S. Hofker, B. van Ramshorst, A.F. Schaapherder. In addition to the authors, the following clinicians participated in the study: *Maastricht University Medical Center, Maastricht* — R.M. van Dam, J.P. Rutten, J.H. Stoot, Y. Keulemans, R. Vliegen; *University Medical Center, Utrecht* — A. Roeterdink, V. Zeguers, U. Ahmed Ali, H.G. Rijnhart, G.A. Cirkel, K.J. van Erpecum, F.P. Vleggaar, M. van Baal, M. Schrijver, L.M. Akkermans, E.J. Hazebroek; *St. Antonius Hospital, Nieuwegein* — M.J. Wiezer, B.L. Weusten, H.D. Biemond; *University Medical Center, Groningen* — R.J. Ploeg, H.T. Buitenhuis, S.U. van Vliet, S. Ramcharan, H.M. van Dullemen; *Academic Medical Center, Amsterdam* — O. van Ruler, W. Laméris, D.J. Gouma, O.R. Busch, P. Fockens; *Leiden University Medical Center, Leiden* — A. Haasnoot, R. Veenendaal; *Gelderse Vallei Hospital, Ede* — B.J. Witteman; *Leeuwarden Medical Center, Leeuwarden* — J.P. Pierie, P. Spoelstra, J.A. Dol, R.T. Gerritsen; *Maasstad Hospital, Rotterdam* — J.F. Lange, N.A. Wijffels, L.A. van Walraven, P.P. Coene, F.J. Kubben; *Amphia Hospital, Breda* — J.H. Wijsman, R.M. Crolla, A.W. van Milligen de Wit, M.C. Rijk; *Reinier de Graaf Hospital, Delft* — L.P. Stassen; *Gelre Hospital, Apeldoorn* — H. Buscher; *St. Elisabeth Hospital, Tilburg* — J. Heisterkamp, H. van Oostvogel, M.J. Grubben; *Canisius–Wilhelmina Hospital, Nijmegen* — A.C. Tan; *Erasmus Medical Center, Rotterdam* — J.B. van der Wal, M.J. Morak, C.J. Pek, J.J. Hermans, E.J. Kuipers, J.W. Poley, M. Bruno; *Radboud University Nijmegen Medical Center, Nijmegen* — J.B. Jansen, S.P. Strijk; *Jeroen Bosch Hospital, Den Bosch* — D. Lips, J.G. Olsman, I.P. van Munster; *Medical Spectrum Twente, Enschede* — J.J. Kolkman, A.B. Huisman; *Medical Center Alkmaar, Alkmaar* — H.A. Tuynman, B.M. Wiarda.

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