Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial

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Summary

Background Infected necrotising pancreatitis is a potentially lethal disease and an indication for invasive intervention. The surgical step-up approach is the standard treatment. A promising alternative is the endoscopic step-up approach. We compared both approaches to see whether the endoscopic step-up approach was superior to the surgical step-up approach in terms of clinical and economic outcomes.

Methods In this multicentre, randomised, superiority trial, we recruited adult patients with infected necrotising pancreatitis and an indication for invasive intervention from 19 hospitals in the Netherlands. Patients were randomly assigned to either the endoscopic or the surgical step-up approach. The endoscopic approach consisted of endoscopic ultrasound-guided transluminal drainage followed, if necessary, by endoscopic necrosectomy. The surgical approach consisted of percutaneous catheter drainage followed, if necessary, by video-assisted retroperitoneal debridement. The primary endpoint was a composite of major complications or death during 6-month follow-up. Analyses were by intention to treat. This trial is registered with the ISRCTN registry, number ISRCTN09186711.

Findings Between Sept 20, 2011, and Jan 29, 2015, we screened 418 patients with pancreatic or extrapancreatic necrosis, of which 98 patients were enrolled and randomly assigned to the endoscopic step-up approach (n=51) or the surgical step-up approach (n=47). The primary endpoint occurred in 22 (43%) of 51 patients in the endoscopy group and in 21 (45%) of 47 patients in the surgery group (risk ratio [RR] 0·97, 95% CI 0·62–1·51; p=0·88). Mortality did not differ between groups (nine [18%] patients in the endoscopy group *vs* six [13%] patients in the surgery group; RR 1·38, 95% CI 0·53–3·59, p=0·50), nor did any of the major complications included in the primary endpoint.

Interpretation In patients with infected necrotising pancreatitis, the endoscopic step-up approach was not superior to the surgical step-up approach in reducing major complications or death. The rate of pancreatic fistulas and length of hospital stay were lower in the endoscopy group. The outcome of this trial will probably result in a shift to the endoscopic step-up approach as treatment preference.

Funding The Dutch Digestive Disease Foundation, Fonds NutsOhra, and the Netherlands Organization for Health Research and Development.

Published Online November 3, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32404-2

See Online/Comment http://dx.doi.org/10.1016/S0140-6736(17)32344-9

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Introduction

Acute pancreatitis is a potentially lethal disease with increasing incidence. Approximately 10–20% of patients develop necrosis of pancreatic parenchyma or extrapancreatic tissues.[1,2] Moreover, about one third of these patients develop infection of the necrotic tissue, which generally requires an invasive intervention.[3]

In the past 10 years, the surgical step-up approach, consisting of percutaneous catheter drainage followed, if necessary, by minimally invasive necrosectomy, has replaced open surgery as the standard treatment.[4,5] A randomised trial of the surgical step-up approach versus primary open necrosectomy showed that catheter drainage as a first step obviates the need for necrosectomy in 35–50% of patients.[4,6]

An endoscopic step-up approach is a potentially less invasive alternative. Endoscopic necrosectomy has shown promising results in reducing complications in several observational studies and one small pilot randomised trial.[7,8] These favourable results were explained by the absence of general anaesthesia and surgical exploration with a reduction of surgical stress and surgery-associated complications such as pancreatic fistulas. The endoscopic approach can also be performed in a step-up fashion, starting with endoscopic transluminal drainage, only to be followed by endoscopic necrosectomy if drainage does not result in clinical improvement.

We did a multicentre randomised trial to investigate whether the endoscopic step-up approach is superior to

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Research in context

Evidence before this study

Before the start of our trial, we did an extensive literature search using PubMed, Embase, and the Cochrane Library database for studies published between Jan 1, 1980, and Dec 31, 2010. We used the search terms "necrosectomy" and "pancreatitis". We included only studies with patients with infected necrosis or symptomatic sterile necrosis, published in English. Studies needed to report the results of patients with infected necrosis separately, as well as mortality and complications. We excluded cohorts with fewer than five patients and studies of patients with chronic pancreatitis. We identified one small pilot trial, 13 cohort studies, and two systematic reviews. The pilot trial of 20 patients compared an endoscopic necrosectomy with a surgical necrosectomy in patients with infected necrosis. This trial was not designed or powered for differences in clinically relevant outcomes but the results suggested a reduced pro-inflammatory response and development of new-onset organ failure after endoscopic necrosectomy. Furthermore, this pilot trial did not incorporate the step-up approaches because it only included patients in whom catheter drainage had failed and subsequently required necrosectomy. The other studies had numerous limitations (ie, small number of patients, retrospective study design, no fixed treatment algorithms, and included patients with sterile necrosis) but they all showed promising results in favour of endoscopic necrosectomy by indirect comparison with surgical necrosectomy. The pilot trial showed significant results by direct comparison.

Added value of this study

To our knowledge, our study is the first high-quality trial to compare an endoscopic step-up approach with the current reference standard of a surgical step-up approach in patients with infected necrosis. Our results are the first to provide level 1 evidence for a reduction in hospital stay and pancreatic fistulas in favour of the endoscopic step-up approach.

Implications of all the available evidence

On the basis of the results of this study, we expect that guidelines will shift from minimally invasive surgery towards endoscopic treatment. Furthermore, treatment of infected necrosis should always take a step-up approach, with endoscopic drainage as the first step. In conclusion, an endoscopic step-up approach reduces pancreatic fistula, length of hospital stay, and costs without any evidence for impaired safety; therefore, this approach should be considered the strategy of choice in patients with infected necrosis.

the surgical step-up approach in patients with infected necrotising pancreatitis.

Methods

Study design and participants

In this multicentre, randomised, superiority trial, we recruited adult (≥18 years of age) patients from seven university medical centres and 12 teaching hospitals of the Dutch Pancreatitis Study Group with a high suspicion or evidence of infection of pancreatic or extrapancreatic necrotic tissues (ie, infected necrosis) with an indication for invasive intervention, for whom both the endoscopic and surgical step-up approach were deemed feasible by a multidisciplinary expert panel. We defined infected necrosis as a positive culture obtained by fine-needle aspiration or the presence of gas within necrotic collections on contrast-enhanced CT. Infected necrosis was suspected in necrotising pancreatitis patients with clinical signs of persistent sepsis or progressive clinical deterioration despite maximal support on the intensive care unit (ICU) without other causes for infection. Key exclusion criteria were previous invasive interventions for necrotising pancreatitis, chronic pancreatitis, and recurrent acute pancreatitis. Further exclusion criteria are given in the appendix (p 4).

All patients or their legal representatives provided written informed consent before randomisation. The study protocol[9] was approved by the institutional review board of the Academic Medical Centre Amsterdam and all other participating centres, and the study was conducted according to this protocol. All authors vouched for the accuracy and completeness of the data and analyses.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to either the endoscopic step-up approach or the surgical step-up approach. Block randomisation with a concealed, fixed block size and stratified by treatment centres was performed centrally by the study coordinators (SvB and JvG) using a web-based randomisation program. Owing to the unfeasibility of masking, all participants and physicians were aware of treatment allocation.

Procedures

An expert panel consisting of 17 experts (nine gastrointestinal surgeons, four gastrointestinal endoscopists, and four radiologists [including MAB, TLB, MJB, VCC, CHD, CHvE, HvG, J-WH, SHH, JSL, KPvL, VBN, J-WP, RT, HGG, and PF]) assessed the indication, timing, and feasibility of both the endoscopic and surgical step-up approaches for all patients.[4] Whenever possible, randomisation and intervention were postponed until 4 weeks after onset of pancreatitis in line with international guidelines.[5]

Treatment strategies were standardised across sites. Patients assigned to the endoscopy group underwent endoscopic ultrasound-guided transluminal (ie, transgastric or transduodenal) drainage with placement of two 7 Fr (2·3 mm diameter) double pigtail stents and

one 8·5 Fr (2·8 mm) nasocystic catheter as the first step. If drainage alone did not lead to considerable clinical improvement, endoscopic transluminal necrosectomy was performed.[9]

Patients assigned to the surgery group underwent radiological CT-guided or ultrasound-guided percutaneous catheter drainage as first step. The preferred route was through the left retroperitoneum with the catheter as guidance for video-assisted retroperitoneal debridement (VARD), if needed. For most collections, this route is the shortest and thereby often the safest. Furthermore, the drain remains retroperitoneal and does not infect the intra-abdominal space.[4,10] If drainage was clinically unsuccessful a VARD procedure was performed.[11]

In both treatment groups, additional endoscopic as well as percutaneous drainage and endoscopic or surgical necrosectomies were allowed. All interventions were done by experienced endoscopists, surgeons, and interventional radiologists. Details on both treatment groups, interventions, postoperative management, and criteria for clinical improvement are in the appendix (pp 4–6).

Routine laboratory tests were done at randomisation and for the 7 consecutive days after, as per daily clinical practice. Follow-up visits were 3 and 6 months after randomisation. Patients were asked to complete a questionnaire, a CT was performed, and exocrine and endocrine pancreatic function were measured (appendix p 6).

Data were collected by local physicians using a standardised case record form (CRF). An independent monitor, unaware of the treatment assignments, checked all endpoints and CRFs with on-site source data. Discrepancies were resolved through consensus among two investigators who were unaware of treatment allocation and not involved in patient care. All CTs were reviewed by an experienced abdominal radiologist (TLB) unaware of the treatment group and outcomes.

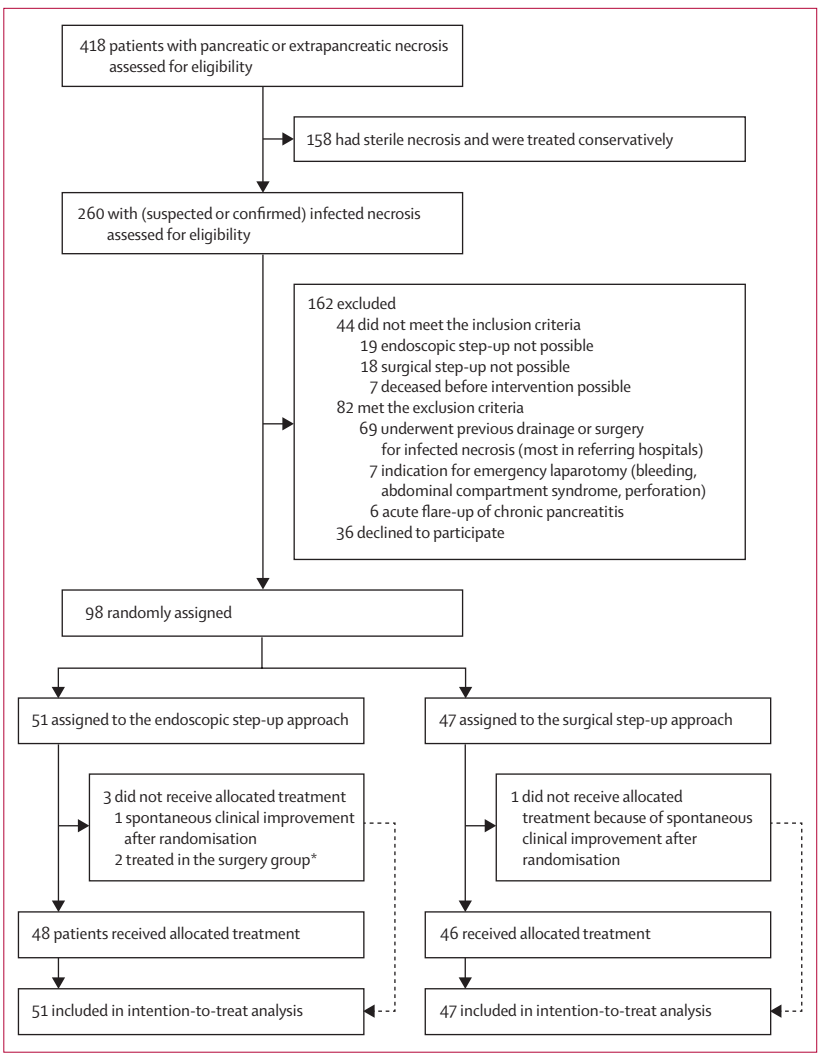

Figure: **Trial profile**
*Endoscopy unsuccessful.

Outcomes

The primary endpoint was a composite of major complications or death within 6 months after randomisation. Major complications were defined as new-onset organ failure (ie, cardiovascular, pulmonary, or renal), bleeding requiring intervention, perforation of a visceral organ requiring intervention (except for the intentionally made perforation during endopscopic treatment), enterocutaneous fistula requiring intervention, and incisional hernia (including burst abdomen). Predefined secondary endpoints included the individual components of the primary endpoint, pancreatic fistula, exocrine and endocrine pancreatic insufficiency, biliary strictures, wound infections, need for necrosectomy, total number of interventions, length of hospital and ICU stay, costs (eg, costs per patient with poor outcome, costs per quality-adjusted life-year [QALY], and total direct and indirect medical costs), quality of life, and the total number of crossovers between groups (for definitions of these primary and secondary endpoints see appendix pp 9–10).

An adjudication committee composed of five surgeons, three endoscopists, and one radiologist performed a blinded outcome assessment. They individually evaluated each patient for the occurrence of the primary endpoint. Disagreements were resolved during a plenary consensus meeting before data analysis started.

After enrolment of each consecutive group of 25 patients, an independent data safety and monitoring committee evaluated the progress of inclusion and safety endpoints for each patient with unblinded data. Patient reports and a list of potential adverse events were presented to the data safety and monitoring committee (see appendix p 7).

Statistical analysis

Based on an expected absolute reduction in the primary composite endpoint of 26% (from 43% to 17%) with a two-sided α of 5%, power of 80%, and 2% loss to follow-up, we

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See **Online** for appendix

	Endoscopic step-up approach (n=51)	Surgical step-up approach (n=47)
Age, years	63 (14)	60 (11)
Female	17 (33%)	18 (38%)
Male	34 (67%)	29 (62%)
Cause of pancreatitis		
Gallstones	26 (51%)	30 (64%)
Alcohol abuse	7 (14%)	7 (15%)
Other*	18 (35%)	10 (21%)
Body-mass index†	29 (25–32)	28 (25–30)
Coexisting condition		
Cardiovascular disease	26 (51%)	18 (38%)
Pulmonary disease	8 (16%)	6 (13%)
Chronic renal insufficiency	4 (8%)	0
Diabetes	11 (22%)	7 (15%)
ASA class on admission		
I: healthy status	17 (33%)	18 (38%)
II: mild systemic disease	29 (57%)	27 (57%)
III: severe systemic disease	5 (10%)	2 (4%)
CT severity index‡	6 (6–8)	8 (6–10)
Extent of pancreatic necrosis		
<30%	26 (51%)	22 (47%)
30–50%	15 (29%)	10 (21%)
>50%	10 (20%)	15 (32%)
Necrosis extending >5 cm down the retrocolic gutters	20 (39%)	22 (47%)
Encapsulation of the necrotic collection		
Partial	15 (29%)	14 (30%)
Complete	36 (71%)	33 (70%)
Gas configurations within the necrotic collection	23 (45%)	27 (57%)
Disease severity§		
Admitted to the ICU at randomisation	21 (41%)	25 (53%)
SIRS¶	33 (65%)	38 (81%)
APACHE II score‖	9 (5–13)	10 (6–13)
APACHE II score ≥20‖	3 (6%)	4 (9%)
Modified Glasgow score**	2 (1–3)	2 (1–3)
Modified MODS score††	0 (0–1)	0 (0–2)
SOFA score††	0 (0–4)	1 (0–3)
C-reactive protein mg/L/‡‡	168 (105–258)	189 (136–301)
White cell count $\times 10^{-9}$ per L§§	14·4 (9·4–18·0)	13·1 (10·5–17·4)
Single organ failure	13 (25%)	14 (30%)
Respiratory	11 (22%)	13 (28%)
Cardiovascular	11 (22%)	7 (15%)
Renal	3 (6%)	1 (2%)
Multiple organ failure	9 (18%)	7 (15%)

(Table 1 continues on next page)

calculated a total sample size of 98 patients. The expected reduction in the primary endpoint in favour of the endoscopic step-up approach was based on the results of various cohort studies, systematic reviews, and a small randomised controlled pilot trial.[7,12–23]

We present results as relative risks with corresponding 95% CIs. We compared dichotomous data with Fisher's exact test, continuous data with the Mann-Whitney *U* test, and categorical data with the linear-by-linear association test.

All primary analyses were by intention to treat. We also did per-protocol analyses. We did a formal test of interaction using logistic regression to assess whether treatment effects differed significantly between predefined subgroups (ie, patients with singular or multiple organ failure at randomisation, academic or non-academic institutions, and time between onset of symptoms and randomisation [<28 *vs* ≥28 days]).

We did no interim analyses. We considered a two-sided p value of less than 0·05 to be statistically significant, and did not adjust p values for multiple testing. Additional details on the statistical analyses are in the appendix (pp 7–8).

We calculated costs as the product sum of the number of resources used and their respective unit costs. Quality-adjusted life-years (QALYs) were calculated as the product sum of EQ-5D-3L-based health utilities at successive measurements during follow-up (3 and 6 months after randomisation) and the lengths of times in between measurements and baseline. We calculated confidence intervals for between-group differences using bias-corrected and accelerated (BCa) bootstrapping, stratified by treatment group and drawing 1000 samples of the same size as the original sample separately for each group and with replacement. Lastly, we did several non-specified post-hoc analyses of the primary endpoints, which are presented in the appendix (p 11).

This trial is registered with the ISRCTN registry, number ISRCTN09186711.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 20, 2011, and Jan 29, 2015, 418 patients with pancreatic or extrapancreatic necrosis in 19 Dutch hospitals were screened, of which 98 were eligible (figure). 51 patients were randomly assigned to the endoscopic step-up approach and 47 to the surgical step-up approach. In each treatment group, one patient did not undergo any intervention because of spontaneous clinical improvement shortly after randomisation. In two other patients in the endoscopy group, owing to the technical difficulty of the drainage procedure, the endoscopist was not able to successfully puncture the collection. These two patients underwent treatment within the surgical step-up approach and were analysed according to the intention-to-treat principle in the

endoscopy group. Baseline characteristics were equally distributed between groups (table 1).

The primary composite endpoint occurred in 22 (43%) patients in the endoscopy group and in 21 (45%) in the surgery group (relative risk 0·97, 95% CI 0·62–1·51; p=0·88; table 2). We observed no significant difference in new-onset single organ failure between groups (table 2); however, new-onset cardiovascular organ failure and persistent cardiovascular organ failure occurred more frequently in the surgery group (table 2). We observed no differences in major complications including bleeding, perforation of a visceral organ, enterocutaneous fistula, and incisional hernia. Mortality was similar in both groups (table 2). The causes of death between both groups did not differ, with most patients dying because of progressive sepsis (two [22%] of nine patients in the endoscopy group, two [33%] of six in the surgery group) and multiple organ failure (four [44%] in the endoscopy group, two [33%] in the surgery group).

The incidence of pancreatic fistulas was lower in the endoscopy group than in the surgery group (table 2). All patients with pancreatic fistulas required persistent drainage during follow-up and nine (60%) of these patients (one patient in the endoscopy group and eight in the surgery group) underwent an additional endoscopic retrograde cholangiopancreatography with pancreatic sphincterotomy or stent placement. At 6-month follow-up, we observed no differences regarding exocrine and endocrine insufficiency, biliary strictures, and wound infections (table 2).

Mean length of hospital stay was 16 days shorter in the endoscopy group compared with the surgery group (table 2). 22 (43%) patients in the endoscopy group and 24 (51%) patients in the surgery group were treated with catheter drainage only (table 2). The remaining patients underwent necrosectomy, occurring sooner in the endoscopy group compared with the surgery group (table 2). More necrosectomy procedures were done in the endoscopy group compared with the surgery group. We observed no difference in the median number of interventions (drainage or necrosectomy) between groups (table 2).

The most common adverse events were pneumonia (16 [31%] patients in the endoscopy group *vs* nine [19%] in the surgery group), bacteraemia (11 [22%] *vs* six [13%]), ascites (seven [14%] *vs* eight [17%]), urinary tract infection (six [12%] *vs* four [9%]), cholecystitis or cholangitis (four [8%] *vs* three [6%]), and atrial fibrillation (three [6%] *vs* two [4%]). All adverse events are listed in the appendix (pp 21–22).

Correction for trends in baseline characteristics (ie, chronic renal insufficiency, systemic inflammatory response syndrome, and modified multiple organ dysfunction syndrome) with multivariable regression analyses did not affect the results (appendix p 26). Predefined subgroup analyses for time of randomisation and institution showed no significant differences in the primary endpoint (appendix p 12). We found no differences in outcome in the subgroup of patients with organ failure at randomisation or after correction for imbalances in baseline in this subgroup. Additional per-protocol analyses did not affect the results, except that persistent cardiovascular organ failure no longer differed between groups (appendix pp 13–14).

	Endoscopic step-up approach (n=51)	Surgical step-up approach (n=47)
(Continued from previous page)		
Time since onset of symptoms, days	39 (28–54)	41 (28–52)
Antibiotic treatment at randomisation	10 (20%)	9 (19%)
Tertiary referral	35 (69%)	35 (74%)
Confirmed infected necrosis¶¶	46 (90%)	46 (98%)

Data are mean (SD), median (IQR), or n (%). ASA=American Society of Anesthesiologists. ICU=intensive care unit. SIRS=systemic inflammatory response syndrome. APACHE=Acute Physiology and Chronic Health Evaluation. MODS=multiple organ dysfunction syndrome. SOFA=Sequential Organ Failure Assessment. *Includes, among others, medication, anatomic abnormalities, and unknown aetiology. †Data missing in 34 patients. ‡Data were derived from the CT performed just before randomisation. Scores range from 0 to 10, with higher scores indicating more extensive pancreatic necrosis and extrapancreatic collections. §Data were based on maximum values during the 24 h before randomisation unless stated otherwise. ¶SIRS was defined according to the consensus-conference criteria of the American College of Chest Physicians and the Society of Critical Care Medicine. ||Scores range from 0 to 71, with higher scores indicating more severe disease. **Scores range from 0 to 8, with higher scores indicating more severe disease. ††Scores range from 0 to 24, with higher scores reflecting more severe organ dysfunction. ‡‡Data missing in 10 patients. §§Data missing in two patients. ¶¶Confirmed infected necrosis was defined as a positive culture of pancreatic or extrapancreatic necrotic tissue obtained by fine-needle aspiration or from the first drainage procedure or operation, or the presence of gas in the collection on contrast-enhanced CT.

Table 1: **Baseline characteristics**

The mean costs of the index interventions (ie, all drainage and necrosectomy procedures) were €3785 in the endoscopy group and €2851 in the surgery group, with a mean difference of €934 (BCa 95% CI –€82 to €2097). The mean total costs per patient from randomisation until 6-month follow-up were €60 228 for the endoscopic step-up approach and €73 883 for the surgical step-up approach. The resulting mean difference of –€13 655 (–€35 782 to €10 836) per patient was not significant.

The number of QALYs gained for the endoscopy group was 0·2788 (BCa 95% CI 0·2458 to 0·3110) compared with 0·2988 (0·2524 to 0·3398) for the surgery group. The mean difference was –0·0199 (–0·0732 to 0·0395). The savings per loss of a single QALY were €684 455. The probability of the endoscopic step-up approach being cost-effective is 0·896 at a societal willingness-to-pay level of €50 000 per QALY (see appendix pp 15–20 for details of the cost analysis).

Discussion

This randomised superiority trial showed that the endoscopic step-up approach was not superior to the surgical step-up approach in reduction of major complications or death in patients with infected necrosis. However, our results showed a benefit in secondary endpoints of endoscopic treatment.

Our results are not in line with a previous small randomised controlled trial,[7] a systematic review,[8] and

	Endoscopic step-up approach (n=51)	Surgical step-up approach (n=47)	Relative risk (95% CI)	p value
Primary endpoint				
Major complications or death*	22 (43%)	21 (45%)	0·97 (0·62–1·51)	0·88
Secondary endpoints				
New-onset organ failure†				
Pulmonary	4 (8%)	7 (15%)	0·53 (0·16–1·68)	0·27
Persistent pulmonary	4 (8%)	5 (11%)	0·74 (0·21–2·58)	0·63
Cardiovascular	3 (6%)	9 (19%)	0·31 (0·09–1·07)	0·045
Persistent cardiovascular	2 (4%)	8 (17%)	0·23 (0·05–1·03)	0·032
Renal	2 (4%)	6 (13%)	0·31 (0·07–1·45)	0·11
Persistent renal	2 (4%)	6 (13%)	0·31 (0·07–1·45)	0·11
Single organ failure	7 (14%)	13 (28%)	0·50 (0·22–1·14)	0·087
Persistent single organ failure	6 (12%)	11 (23%)	0·50 (0·20–1·25)	0·13
Multiple organ failure	2 (4%)	6 (13%)	0·31 (0·07–1·45)	0·11
Persistent multiple organ failure	2 (4%)	5 (11%)	0·37 (0·08–1·81)	0·20
Bleeding (requiring intervention)	11 (22%)	10 (21%)	1·01 (0·47–2·17)	0·97
Perforation of a visceral organ or enterocutaneous fistula (requiring intervention)	4 (8%)	8 (17%)	0·46 (0·15–1·43)	0·17
Incisional hernia	0	1 (2%)	..	0·30
Death	9 (18%)	6 (13%)	1·38 (0·53–3·59)	0·50
Other endpoints‡				
Pancreatic fistula	2/42 (5%)	13/41 (32%)	0·15 (0·04–0·62)	0·0011
Exocrine insufficiency				
Use of enzymes	16/42 (38%)	13/41 (32%)	1·20 (0·66–2·17)	0·54
Fecal elastase <200 mg/g	22/42 (52%)	19/41 (46%)	1·13 (0·73–1·75)	0·58
Steatorrhoea	6/42 (14%)	7/41 (17%)	0·84 (0·31–2·28)	0·73
Endocrine insufficiency	10/42 (24%)	9/41 (22%)	1·08 (0·49–2·39)	0·84
Biliary strictures	3 (6%)	3 (6%)	0·92 (0·20–4·34)	0·92
Wound infections	2 (4%)	3 (6%)	0·61 (0·11–3·52)	0·58

(Table 2 continues on next page)

observational studies[24,25] suggesting clinical superiority of endoscopy. Several possible explanations exist for the differing outcome. First, observational studies have a risk of confounding by indication and most of these studies did not have a well defined study protocol or clearly described treatment algorithms. Furthermore, patients with sterile collections were also included in some of these studies, which could have led to comparisons of less severe cases with patients with infected necrosis. In our trial, inclusion criteria were strict and were confirmed by an expert panel.

Second, in line with a previously proposed hypothesis, the previous small trial[7] showed that endoscopic treatment led to a less severe pro-inflammatory response and, subsequently, fewer occurrences of new organ failure compared with surgery. These results were also not confirmed in our trial. Although we did not measure the pro-inflammatory response, new-onset single organ failure as a clinical manifestation of immune response did not differ between groups. However, both cardiovascular and persistent cardiovascular organ failure were lower in the endoscopy group. This difference could be the result of the differing designs of both studies. The previous trial[7] compared an endoscopic necrosectomy with a surgical necrosectomy instead of two step-up approaches as in our trial. This trial design also explains the inclusion of more severely ill patients (ie, patients in whom percutaneous drainage failed) in the previous trial.[7] Moreover, 40% of the surgical patients in the previous study[7] received open necrosectomy as opposed to VARD, whereas in our trial no patients underwent an open necrosectomy. This difference is important because open necrosectomy is thought to be associated with more complications than is VARD.

Third, patients in our trial were more severely ill than those included in the previous trial[7] in terms of ICU stay, presence of systemic inflammatory response syndrome, single or multiple organ failure at randomisation, and the high percentage of patients with confirmed infected necrosis compared with the patients included in previous observational studies.

Finally, our sample size could still have been too small. The number of patients needed was based on the results of small, mostly observational studies. A small sample size might therefore have overestimated the effect of endoscopic treatment.

51% of surgical patients were successfully treated with catheter drainage only. This result is higher than the 35% successfully treated in a previous randomised trial,[4] but comparable with a published systematic review.[6] We found that more than 40% of patients in the endoscopy group were also successfully treated with endoscopic drainage only without additional necrosectomy. Previous research has identified male sex, multiple organ failure, increasing percentage of pancreatic necrosis, and heterogeneity of the collection as negative predictors for success of percutaneous catheter drainage in infected necrotising pancreatitis.[26] The total number of necrosectomy procedures in both treatment groups are in line with published data.[4,7]

During the inclusion period, 37 (14%) of 260 patients were excluded because either the endoscopic or surgical approach was deemed not possible. As with percutaneous drainage, endoscopic drainage was feasible in almost all patients included (96%). 14 (27%) of 51 patients in the endoscopy group needed additional percutaneous catheter drainage mostly when necrosis was extending down retroperitoneally into the pelvis. Despite the need for additional percutaneous drainage, the incidence of pancreatic fistulas was significantly lower in the endoscopy group. All recorded pancreatic fistulas were external (ie, pancreaticocutaneous fistulas). These fistulas might account for serious morbidity (ie, pain, loss of pancreatic juices), additional interventions, extended hospital stay, and intensified follow-up. So-called internal pancreatic fistulas probably also occurred in the endoscopy group. These internal fistulas, how-

ever, are deemed less clinically relevant than external pancreatic fistulas.

The interval between the first drainage and first necrosectomy was notably shorter in the endoscopy group than in the surgery group. This result could be due to a potentially higher threshold in the surgery group to proceed to VARD after catheter drainage compared with the threshold in the endoscopy group to proceed to endoscopic necrosectomy. Additional necrosectomy after endocopic drainage is a relatively small step, done by the same specialist via the same route. The step from catheter drainage to VARD in the surgery group was larger, with the surgeon performing the minimally invasive surgical necrosectomy after previous drainage done by the radiologist. Furthermore, compared with the endoscopy group, drains in the surgery group were more often repositioned and upsized, and multiple drains were placed more often.[27] This argument is supported by the difference in patients treated with solely catheter drainage in the surgery group between a previous trial[4] (35%) and our current study (50%), indicating more extensive and better drainage in our study. Moreover, percutaneous drains have a larger diameter and potentially clog less frequently than do endoscopic catheters. These aspects of the surgical step-up approach might have resulted in a prolonged effect of percutaneous drainage, delay of necrosectomy, and, subsequently, prolonged hospital stay.

During the course of the trial, short lumen-apposing fully-covered metal stents were introduced into the medical armatorium, which are gaining popularity in endoscopic treatment. The larger diameter compared with the plastic pigtail stents that were used in this trial potentially leads to better drainage and, hypothetically, fewer necrosectomies. Disadvantages might be migration of the stent, bleeding, perforation, and stent overgrowth.[28–31] In view of insufficient evidence of significant benefit of metal stents over plastic pigtail stents, we decided to use the well studied pigtail stents during the entire study.

Our study has some limitations. First, as mentioned, our sample size was still relatively small. However, because no trends for differences in mortality were seen, a larger trial is unlikely to find a significant difference in mortality. Second, almost one third of patients in the endoscopy group underwent additional percutaneous drainage. Because this was a pragmatic trial, percutaneous drainage was allowed, as would be done in clinical practice in these patients. Third, follow-up was 6 months after randomisation. This length could be too short to detect further benefits or complications of the endoscopic step-up approach on the long term.

Treatment of infected necrosis is complex and mortality remains high despite treatment techniques becoming progressively less invasive and more tailored. In clinical practice, the endoscopic step-up approach is gaining popularity alongside the surgical step-up approach. Our study has shown that both approaches are valid treatment options, although an important clinical advantage of the endoscopic approach is the reduction in external pancreatic fistulas and hospital stay. In our view, patients with infected necrosis should be treated in tertiary referral centres by multidisciplinary teams where both the endoscopic and surgical step-up approach are available, because a combined approach might be required in some patients. Based on current findings, the first step of step-up treatment will most likely be endoscopic, if several options are available. In the future, a tailored approach based on patient characteristics, location of collections, and degree of encapsulation will probably become the new standard.

	Endoscopic step-up approach (n=51)	Surgical step-up approach (n=47)	Relative risk (95% CI)	p value
(Continued from previous page)				
Health-care use				
Median number of interventions§	3 (2–6)	4 (2–6)	..	0·35
Drainage procedures¶	1 (1–3)	3 (1–5)	..	0·0041
Necrosectomies‖	2 (1–4)	1 (1–1)	..	0·0004
Number of necrosectomies	..	..	..	0·0062
0	22 (43%)	24 (51%)	0·84 (0·55–1·29)	..
1	9 (18%)	18 (38%)	0·46 (0·23–0·92)	..
2	8 (16%)	3 (6%)	2·46 (0·69–8·72)	..
≥3	12 (24%)	2 (4%)	5·53 (1·31–23·42)	..
Additional percutaneous drainage in the endoscopy group	14 (27%)	..	..	..
Additional VARD procedure in the endoscopy group	2 (4%)	..	..	..
Additional endoscopic drainage in the surgical group	..	2 (4%)	..	..
Additional endoscopic necrosectomy in the surgical group	..	0	..	..
Days between first drainage and first necrosectomy				
Median (range)	10 (5–16)	23 (9–62)	..	0·013
Mean (SD)	14 (14)	33 (30)	..	..
Days in ICU within 6 months of randomisation**				
Median (IQR)	0 (0–3)	2 (0–11)	..	..
Mean (SD)	13 (31)	13 (21)	..	0·31
Days in hospital within 6 months of randomisation				
Median (IQR)	35 (19–85)	65 (40–90)	..	..
Mean (SD)	53 (47)	69 (38)	..	0·014

Data are n (%), mean (SD), or median (IQR) unless otherwise stated. Relative risk is reported for dichotomous variables for the endoscopic step-up approach as compared with the surgical step-up approach. ICU=intensive care unit. VARD=video-assisted retroperitoneal debridement. *Multiple events in the same patient were considered as one endpoint. †Organ failure occurring after randomisation and not present 24 h before randomisation. ‡Patients were assessed 6 months after randomisation; patient deaths were excluded. §This category included all drainage procedures (endoscopic or percutaneous) and necrosectomies (endoscopic or VARD) as part of the endoscopic or surgical step-up approach. ¶This category included primary drainage procedures (endoscopic or percutaneous) as part of the endoscopic or surgical step-up approach and additional drainage procedures before and after necrosectomy in both treatment groups. ‖This category included all necrosectomies (endoscopic or VARD procedure) as part of the endoscopic or surgical step-up approach. **For patients not present in ICU 24 h before randomisation.

Table 2: **Primary and secondary endpoints according to the intention-to-treat analysis**

In conclusion, this multicentre randomised trial did not show the hypothesised superiority of the endoscopic step-up approach in reducing major complications or death in patients with infected necrosis, although the number of pancreatic fistulas and total hospital stay were lower in the endoscopy group.

Contributors

SvB did the statistical analysis and drafted the manuscript. MGD supervised the economic evaluation. HCvS, JvG, OJB, MGB, HGG, MGD and PF co-authored the manuscript. SvB, HCvS, MGB, OJB, RPV, MGD, MAB, MJB, TLB, RT, HGG, and PF contributed to designing of the study before and during several meetings of the Dutch Pancreatitis Study Group. SvB, HCvS, RPV, and MGD calculated the sample size. SvB and JvG coordinated the study during inclusion. All authors critically assessed the study design or included patients in the study and edited, read, and approved the final manuscript.

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Declaration of interests

We declare no competing interests.

Acknowledgments

The Dutch Digestive Disease Foundation (Maag Lever Darm Stichting, grant number WO 09-45), Fonds NutsOhra (grant number 1101-108), and the Netherlands Organization for Health Research and Development Health Care Efficiency Research programme (ZonMw, grant number 837004008) financially supported this trial.

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