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# Superiority of Step-up Approach vs Open Necrosectomy in Long-term Follow up of Patients With Necrotizing Pancreatitis

**Short title: Long-term Results of the Step-up Approach for Necrotizing Pancreatitis**

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**Abbreviations:** CI: Confidence interval; EQ-5D: Euroqol 5 dimensions; IQR: Interquartile range; M-ANNHEIM: Pancreatitis with multiple risk factors: Alcohol, Nicotine, Nutritional, Hereditary, Efferent duct, Immunological, Miscellaneous; SD: Standard deviation; SF-36: Short form 36

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**Disclosures:** None reported

## Author contributions

RAH: study concept and design, acquisition of data, interpretation of data, statistical analyses, drafting and critical revision of the manuscript for intellectual content; OJB, MAB, TLB, KB, CHD, PD, CHE, WMUG, EH, JH, EJH, SH, APH, TK, PMK, CJL, ERM, IQM, VBN, BR, DR, CR, AFS, GPS, RT, RJW: Facilitating acquisition of data, interpretation of data, critical revision of the manuscript for intellectual content; MJB, PF, HG, RCV, HGG, MGB: Study concept and design, facilitating acquisition of data, interpretation of data, critical revision of the manuscript for intellectual content; EB, JSL, MSL: revising the manuscript; HCS: study concept and design, acquisition of data, interpretation of data, statistical analyses, drafting and critical revision of the manuscript for intellectual content, principal investigator.

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**ABSTRACT**

**Background and aims**

In a 2010 randomized trial (the PANTER trial), a surgical step-up approach for infected necrotizing pancreatitis was found to reduce the composite endpoint of death or major complications compared with open necrosectomy; 35% of patients were successfully treated with simple catheter drainage only. There is concern, however, that minimally invasive treatment increases the need for reinterventions for residual peripancreatic necrotic collections and other complications during the long term. We therefore performed a long-term follow-up study.

**Methods**

We re-evaluated all the 73 patients (of the 88 patients randomly assigned to groups) who were still alive after the index admission, at a mean 86 months (±11 months) follow up. We collected data on all clinical and health care resource utilization endpoints through this follow-up period. The primary endpoint was death or major complications (the same as for the PANTER trial). We also measured exocrine insufficiency, quality of life (using the SF-36 and EQ-5D forms) and Izbicki pain scores.

**Results**

From index admission to long-term follow up, 19 patients (44%) died or had major complications in the step-up group compared with 33 patients (73%) in the open-necrosectomy group (*P*=.005). Significantly lower proportions of patients in the step-up group had incisional hernias (23% vs 53%; *P*=.004), pancreatic exocrine insufficiency (29% vs 56%; *P*=.03), or endocrine insufficiency (40% vs 64%; *P*=.05). There were no significant differences between groups in proportions of patients requiring additional drainage procedures (11% vs 13%; *P*=.99) or pancreatic surgery (11% vs 5%; *P*=.43), or in recurrent acute pancreatitis, chronic pancreatitis, Izbicki pain-scores, or medical costs. Quality of life increased during follow up without a significant difference between groups.

**Conclusions**

In an analysis of long-term outcomes of trial participants, we found the step-up approach for necrotizing pancreatitis to be superior to open necrosectomy, without increased risk of reinterventions.

**Keywords**

Pancreas; infected necrosis; minimally invasive, pancreatic surgery

**Background and aims**

Infected necrotizing pancreatitis typically requires invasive intervention.[1,2] Traditionally, primary open necrosectomy with extensive debridement and post-operative lavage was the preferred treatment. In the last 3 decades, minimally invasive catheter drainage and necrosectomy methods have become increasingly popular.[3] In 2010, we published the first randomized controlled trial (the PANTER trial) on invasive treatment for infected necrotizing pancreatitis.[4] We compared primary open necrosectomy with a novel surgical step-up approach in 88 patients with necrotizing pancreatitis. The step-up approach consisted of primary percutaneous catheter drainage, followed, if necessary, by minimally invasive retroperitoneal necrosectomy. The step-up approach aims to provide source control, rather than complete removal of the infected necrotic tissue. This decreases the pro-inflammatory response induced by surgical trauma, which may prevent further clinical deterioration and may obviate the need for necrosectomy. The step-up approach significantly reduced the composite primary endpoint of major complications and death (risk ratio 0.57). Also, 35% of patients assigned to the step-up group were successfully treated with percutaneous catheter drainage only. The secondary endpoints of incisional hernia, new-onset diabetes, use of pancreatic enzymes and total costs at 6 months follow up were also reduced in the step-up group.[4] International guidelines now advocate a surgical or endoscopic step-up approach as standard treatment of infected necrotizing pancreatitis.[1,5-8]

The two treatment strategies compared in the PANTER trial differ fundamentally in terms of anatomical approach and the extent in which necrotic material is removed. In a third of all patients from the step-up approach, only infected fluid was drained from the collection and necrosis was left *in situ.* As a result, patients who initially recovered from their sepsis without necrosectomy may have developed symptoms and complications from residual peripancreatic collections with necrosis that require percutaneous, endoscopic, or surgical interventions beyond the initial 6 months follow up of the trial. Repeated re-admissions and disease burden from other long-term complications such as incisional hernias, pancreatic insufficiency, or persisting abdominal pain may also differ between the step-up approach and primary open necrosectomy. In general, post-trial follow-up studies of randomized trials are regarded to be important to detect long-term differences in safety and efficacy outcomes.[9] We therefore performed a study, 86 months after the first analysis of the PANTER trial, to compare the long-term follow up of the step-up approach with primary open necrosectomy in terms of clinical outcomes, healthcare utilization and quality of life.

## Methods

*Patients and treatment during follow up*

Between November 2005 and October 2008, 88 patients with (suspected or confirmed infected) necrotizing pancreatitis were randomly assigned to the step-up approach (n=43) or primary open necrosectomy (n=45). In total, 15 patients died during the PANTER trial, 8 patients in the step-up group and 7 in the open-necrosectomy group, leaving a total of 73 patients eligible for long-term follow up.[4] Diagnostics and treatment beyond the initial follow up of 6 months were not defined by protocol of the PANTER trial and was performed at the discretion of the treating physician.

*Timeline*

Final discharge date of the last admitted patient during the PANTER trial was on January 19, 2009. Ethical approval for the current nationwide follow-up study in the original 19 Dutch hospitals participating in the PANTER trial was given by the medical ethics committee of the University Medical Center Utrecht by the end of October 2013. After primary contact, follow-up visits of patients were planned between June 2014 and January 2015. Additional data collection at referring hospitals, general practitioners and pharmacies was concluded by the end of 2015.

*Procedure of Follow up*

After written informed consent was provided, patients were invited to an outpatient visit in the hospital where they were treated during the PANTER trial. If patients were unable to attend, the coordinating investigator (RAH) visited patients at home. During visits, recorded medical history during follow-up years was verified, with special attention to hospital re-admittance (in particular in hospitals other than in which the patient was initially treated), endoscopic or surgical interventions, gastrointestinal complaints, pain and medication (i.e. pancreatic enzymes, oral antidiabetics and insulin). Before the follow-up visit, patients received validated quality of life questionnaires (EQ-5D[9] and SF-36[10]) to fill out at home. Physical examination was performed with special attention to the abdomen. Stool samples were collected to evaluate exocrine pancreatic function. Medical information of patients who died during follow up was collected from hospital records and through contact with general physicians and contact with relatives.

*Clinical Outcomes*

In accordance with the PANTER trial, the primary endpoint of the current study was a composite of death or major complications; i.e. new-onset multiple organ failure or systemic complications, enterocutaneous fistula or perforation of a visceral organ requiring intervention, or intra-abdominal bleeding requiring intervention at any time during follow up.[4] All the individual components of the primary endpoints were assessed by the individual members the original adjudication committee that also adjudicated the primary endpoint of the PANTER trial. The committee was blinded for treatment assignment.

Individual components of the primary endpoint were evaluated separately as secondary endpoints. Other secondary end-points included pancreatic fistula, incisional hernias, recurrent pancreatitis, chronic pancreatitis according to the M-ANNHEIM diagnostic criteria[11], endoscopic pancreatic intervention, pancreatic surgery, and other related surgical procedures after the index admission (i.e. surgical hernia repair, colostomy reversal and cholecystectomy). New onset pancreatic endocrine insufficiency was defined as the need for treatment for glycemic control with oral antidiabetics or insulin. Pancreatic exocrine insufficiency was measured in a single stool sample using Schebo Biotech KIT (Elisa). Exocrine insufficiency was defined as a fecal elastase-1 level of <200 µg/g feces.[12,13] Patient reported medicine use for endocrine or exocrine insufficiency was verified through contact with general practitioners and/or pharmacies.

The clinical outcomes are presented for both the long-term follow-up months (i.e. the months following the initial 6 month follow up included in the trial phase analyses) and the overall follow-up period (i.e. from index admission to long-term follow up) for easy comparison and correct interpretation.

*Quality of Life and Pain*

Quality of life scores were obtained by 2 validated questionnaires; the short form 36-item health survey (Medical Outcomes Trust, Boston, MA)[10] and the EuroQol health status profile.[9,14] Both questionnaires are implemented in the Dutch health care system by previous translation and validation.[15,16] Patients filled out both questionnaires at 3, 6 and 12 months after discharge from index (i.e. randomization) admission. At long-term follow up, patients received the same questionnaires enabling comparison

over time. Results are presented as the physical component and mental component summary measures according to US and Dutch standards.[10]

In chronic pancreatitis, the Izbicki pain score is a common tool to assess intensity and frequency of pain attacks, use of pain medication and restriction from daily activities.[17] No such tool is available for acute pancreatitis. We therefore used the Izbicki pain score in our follow-up interviews for assessment of abdominal pain and impact on daily life.

*Cost Analysis*

Utilization of health care resources during the entire follow-up period was evaluated. Variables included days of admittance to hospitals (i.e. general ward, intensive care unit), diagnostic procedures, therapeutic interventions (i.e. interventional radiology, endoscopy, surgery), outpatient visits/contacts (i.e. specialists and nurses), general physician care and use of medication for pancreatic endocrine and exocrine insufficiency. A cost analysis from a medical perspective was performed to estimate if the difference in costs remained in favor of the minimally invasive step-up group during long-term follow up. For prize-calculations we used inflation corrected cost-estimations used during the PANTER trial and other trials from our study group. For reference values we consulted cost indicator lists provided online by the Dutch Care Authority.[18,19] Missing values were calculated manually in collaboration with the financial department of the St. Antonius Hospital, Nieuwegein, the Netherlands.

*Statistical Analysis*

Analyses were performed according to the principles of intention-to-treat. Outcome measures are presented as mean ± standard deviations (SD) or median and interquartile ranges (IQR) as appropriate. For statistical significance of continuous variables, the independent sample t-test or Mann-Whitney U test were used as appropriate. For categorical data the Chi-square test was used and in case of small numbers, the Fisher's exact test. Cost analyses are presented as mean costs per patient per year and mean difference with associated 95% confidence interval (CI). Quality of life scores are compared between treatment groups by the independent sample t-test and within treatment groups by linear mixed models with unstructured repeated covariance. Data analyses were performed using SPSS 22.0 (IBM Corp. Armonk, NY). P-values $<0.05$ were considered statistically significant.

## Results

*Follow up and clinical endpoints*

Mean follow up was 86 months (± 11 months) after discharge from the index admission. During the PANTER trial, 15 out of 88 included patients died. During the long-term follow-up period another 7 patients died. Long-term follow up was completed actively (i.e. personal contact, stool sample, quality of life questionnaires) in 61 out of 66 surviving patients and passively in 5 surviving and 7 deceased patients (i.e. retrospective data collection; Figure 1). Baseline variables were comparable between the step-up and open-necrosectomy group during the trial.[4]

Clinical end points are given in Table 1. From the index admission to long-term follow up, the primary endpoint occurred in 19 (44%) patients assigned to the step-up group and in 33 (73%) patients assigned to the open-necrosectomy group ($P$ = 0.005; Table 1, Figure 2). During the long-term follow up, in the step-up group, 1 patient died after early multiple organ failure during an episode of recurrent acute pancreatitis. A further 4 deaths occurred in the step-up group which were unrelated to pancreatitis: 1 due to stroke, 1 due to metastatic prostate cancer, 1 due to a ruptured abdominal aortic aneurysm and 1 most likely due to cardiac arrest. In the open-necrosectomy group, 1 patient died after severe intra-abdominal bleeding after endoscopic transluminal drainage of a residual, symptomatic pancreatic fluid collection. A second patient from the open-necrosectomy group died following metastatic esophageal cancer.

During long-term follow up, five patients had a persistent pancreatic fistula. All 5 patients were from the step-up group, of whom 4 patients initially underwent videoscopic assisted retroperitoneal debridement. Fistula resolved spontaneously in 1 patient, were treated by ERCP and stenting in 2 patients and by pancreatic surgery in 2 patients, 7 to 32 months after index intervention. Overall, 34 patients had an incisional hernia resulting from the initial pancreatic necrosectomy, for which 18 patients (6 patients from the step-up group) underwent surgical correction at a mean of 25 months after primary surgery.

Endocrine insufficiency developed in 42 patients during the entire period of original and long-term follow up (Table 1). In 19 patients, this was treated with oral antidiabetics alone, in 9 patients with insulin alone and in 14 patients with both oral antidiabetics and insulin. In 3 patients, endocrine insufficiency resolved during follow up. Overall, 26 patients used pancreatic enzyme supplements (Table 1), of whom 6 discontinued taking these enzymes (2 from the step-up group) during follow up.

*Survivors at long-term follow up*

At the long-term follow up, 66 patients (30 patients from the step-up group) out of the 88 randomized patients (75%) were alive. Outcomes are summarized in Table 2. Fourteen patients (21%) experienced recurrent episodes of acute pancreatitis of whom 6 patients developed chronic pancreatitis. One other patient, who was not readmitted for recurrent acute pancreatitis also developed chronic pancreatitis (total: 7 patients; 11%). Pancreatic endocrine insufficiency was present in 12 (40%) patients from the step-up group and 23 (64%) patients from the open-necrosectomy group (*P* = 0.053). According to the fecal elastase-1 test, exocrine insufficiency was present in 29% and 58% respectively (*P* = 0.03). At long-term follow up, 5 (17%) patients from the step-up group and 14 (39%) patients from the open-necrosectomy group used supplemental pancreatic enzymes (*P* = 0.047), of whom 2 and 9 patients respectively had pancreatic exocrine insufficiency according to their fecal elastase-1. The test was not performed in 1 patient in each group.

Subjective abdominal complaints and Izbicki pain scores are summarized in Table 2. In 8 patients (4 from each group) with pancreatic exocrine insufficiency and in 16 patients (11 patients from the step-up group) without pancreatic exocrine insufficiency, no complaints were reported and no supplemental enzymes were used at long-term follow up. Of the 5 patients (all from the step-up group) who had complaints of steatorrhea, 1 patient used supplemental pancreatic enzymes and only 1 (other) patient had a fecal elastase-1 level of less than 200µg/gram. There were no statistically significant differences in Izbicki pain scores between treatment groups.

*Quality of life*

Quality of life was measured at approximately 3, 6 and 12 months after discharge from index admission and at long-term follow up. Detailed results are given in Supplementary Table 1, including the results at long-term follow up, which are also summarized in Table 3. There were no significant differences between treatment groups at any of the 4 time-points.

The SF-36 physical component score (Dutch standard) increased significantly during the first year of follow up (step-up: 36 ± 8 at 3 months, to 46 ± 9 at 1 year (*P* = <0.01); open: 40 ± 12 at 3 months to 44 ± 13 at 1 year (*P* = 0.04)), after which it remained stable, as compared with the long-term follow up in both treatment groups. The physical component scores at long-term follow up did not

reach the general population scores of 50 ± 10. The SF-36 mental component score (Dutch standard) increased slightly during follow up in both treatment groups. At long-term follow up, the SF-36 mental scores (step-up: 47 ± 11; open: 48 ± 11) approximated the general population scores of 50 ± 10.[10]

The EQ-5D scores significantly increased during the entire follow up in the step-up group (0.64 ± 0.26 at 3 months to 0.81 ± 0.21 at long-term follow up; $P < 0.01$). The increase in the open-necrosectomy group (0.70 ± 0.27 at 3 months to 0.75 ± 0.30 at long-term follow up) was lower and was not statistically significant. The perceived health score increased up to 1 year after follow up in the step-up group (65 ± 15 at 3 months and 75 ± 17 at 1 year; $P = 0.03$) and remained stable in the open-necrosectomy group (70 ± 14 at 3 months and 71 ± 16 at 1 year; $P = 0.44$), after which it decreased to equal values at long-term follow up (70 ± 19 and 69 ± 20 respectively). The increasing slopes over time in all quality of life scores did not differ significantly between the step-up group and the open-necrosectomy group (Supplementary Table 2). Considering all patients at long-term follow up, all quality of life scores measured were significantly lower in patients who reported abdominal pain (i.e. Izbicki score > 0), as compared with patients who did not report pain (Supplementary Table 3). Quality of life scores at the end of follow up did not differ significantly between patients with 1 or more subjective abdominal complaints, as compared with patients without abdominal complaints. There was also no difference between patients with or without endocrine or exocrine insufficiency (Supplementary Tables 4 to 7).

*Health care resource utilization*

Invasive pancreatic interventions, surgical procedures directly or indirectly related to necrotizing pancreatitis and hospital admission during the study period are presented in Table 4. Pancreatic surgery is further specified in Supplementary Table 8. During long-term follow up, 9 patients underwent catheter drainage of a residual symptomatic pancreatic fluid collection at a mean of 23 months after index intervention; 3 patients underwent percutaneous drainage (2 patients from the step-up group) and 6 patients underwent endoscopic transluminal drainage (2 patients from the step-up group). These 9 patients had previously undergone necrosectomy. Among patients who underwent catheter drainage of a pancreatic fluid collection or pancreatic surgery during long-term follow up, 8 patients had (clinical/radiological) signs of (partly) disconnected pancreatic duct due to gland necrosis

with a vital remnant tail section. Details on diagnosis and treatment of these patients are provided in Supplementary Table 9.

Costs are presented in Supplementary Table 10. During long-term follow up, the difference in overall medical costs between treatment groups was not statistically significant.

## Discussion

We studied the clinical outcomes, quality of life and health care utilization in 73 patients during long-term follow up after randomization to a surgical step-up approach or primary open necrosectomy as treatment for necrotizing pancreatitis. Overall, the step-up approach reduced the primary endpoint of death or major complications, as compared with primary open necrosectomy. Incisional hernias were more frequent in the primary open-necrosectomy group, as was pancreatic exocrine insufficiency. Also, there was a trend towards a higher prevalence of pancreatic endocrine insufficiency in the open-necrosectomy group. During long-term follow up, no differences in rates of pancreatic interventions, number of re-admissions, quality of life or medical costs were seen between the two groups. External pancreatic fistulas that persisted beyond 6 months after discharge from the index admission were only observed in the step-up group.

All patients assigned to the primary open-necrosectomy group underwent 1 or more necrosectomy procedures during the index admission and initial 6 months follow-up period of the trial. In the step-up group, 35% of patients undergoing catheter drainage recovered without further necrosectomy. In patients treated with catheter drainage only, residual pancreatic necrosis or necrotic collections could have become symptomatic, which would have required additional invasive interventions beyond the 6 months of follow up as defined in the original protocol of the PANTER trial. In the current long-term follow-up study, only 2 of the patients who initially recovered with catheter drainage only, underwent additional pancreatic surgery. In total, 4 patients from the step-up group and 2 patients from the open-necrosectomy group underwent pancreatic surgery during long-term follow up. In general, the need for additional surgery following the initial episode of necrotizing pancreatitis was low, and in line with 2 other studies on invasive interventions during long-term follow up after necrotizing pancreatitis.[20,21] A minimally invasive step-up approach thus appears to be equally effective as a primary open necrosectomy in treating sepsis during the primary episode of infected necrotizing pancreatitis, without an increased risk of additional radiological or surgical interventions during long-term follow up. Moreover, attributed to the minimally invasive approach, there were fewer incisional hernias in the step-up group, leading towards a trend in fewer surgical incisional hernia repairs.

Functional endocrine and exocrine impairment of the pancreas following an episode of necrotizing pancreatitis has been evaluated in several meta-analyses.[22,23] Studies comparing

minimally invasive approaches with open necrosectomy, however, focused mainly on short-term, clinical end-points and did not perform a long-term follow up with regard to pancreatic function.[24-26] Our study showed a clear overall lower rate of pancreatic enzyme use in the step-up group. This was already apparent at the initial 6 months follow up and did not increase further during subsequent years. At long-term follow up, a significantly greater number of patients in the open-necrosectomy group had fecal elastase-1 levels below the threshold of 200µg/gram and twice as many used supplemental pancreatic enzymes. These findings are new, as fecal elastase testing was not performed routinely in the original study. Overall, no difference in the number of patients using antidiabetic medication was seen between groups. At long-term follow up, however, there was a trend towards a lower incidence of antidiabetic medication use in the step-up group. Altogether, our findings suggest that the step-up approach preserves pancreatic parenchyma and function, as compared with primary open necrosectomy. The beneficial difference for the step-up approach becomes apparent shortly after recovery of the disease and remains constant during the long-term.

Our study is the first to compare quality of life following two different methods of invasive intervention for necrotizing pancreatitis. We found a significant improvement in quality of life in the physical state (SF-36 questionnaire) during the first year in both treatment groups, which is in line with a previous longitudinal study in 21 patients with necrotizing pancreatitis treated in the intensive care unit.[27] The generic health score (EQ-5D questionnaire) increased gradually over time in both treatment groups, but the increase in the step-up group was more prominent. The step-up group started with a lower score at 3 months, which may be attributable to the physical disability because of continued percutaneous catheter drainage. Subsequently, a more rapid increase in their physical state was seen between 3 and 6 months. However, at none of the measurement time points, the difference between the treatment groups was statistically significant. Quality of life at long-term follow up did not differ between patients with and without endocrine or exocrine pancreatic insufficiency, which is noteworthy as these conditions impose the burden of using daily medication, dietary changes and the consciousness of physical illness. As patients get accustomed to the daily adaptations necessary to regulate their disease, they apparently perceive a similar quality of life, as compared with patients without endocrine or exocrine insufficiency.

During the initial 6 months follow up of the PANTER trial, the step-up approach reduced costs by 12%.[4] During long-term follow up there was no difference in overall medical costs per patient per

year between the treatment groups in our detailed, medical perspective cost analysis. However, in line with the higher prevalence of exocrine insufficiency and the trend towards more endocrine insufficiency of survivors at long-term follow up in the open-necrosectomy group, a trend of higher annual costs for pancreatic enzyme replacement therapy and antidiabetics per patient in the open-necrosectomy group was observed. This is particular noteworthy because the worldwide incidence of acute pancreatitis and health care costs are increasing.[28]

This study is unique as it is the first to describe the long-term follow up of a randomized trial comparing two fundamentally different invasive intervention strategies for necrotizing pancreatitis. We performed a thorough prospective follow up on clinical end-points, health care utilization and quality of life. Nonetheless, a few issues need to be addressed. First, our definition of endocrine insufficiency was based on the use of antidiabetic medication instead of a serum glucose test. Although, in the Netherlands, patients in the follow up of severe necrotizing pancreatitis are regularly checked on blood glucose levels, impaired glucose intolerance without overt signs and symptoms of diabetes in patients not using antidiabetics could have been missed. Second, quality of life questionnaires were not collected annually after the first year. This resulted in a large gap of approximately 6 years between the last 2 measurement moments. In theory, a potential clinically significant difference in quality of life between both treatment groups in the intermediate years may have gone by unnoticed. Studies show that, as time goes by, patients tend to become accustomed to their physical impairment. As a result, quality of life may become comparable between treatment groups at long-term follow up.[29] Third, although detailed, our long-term cost analysis was limited to the medical perspective and did not include visits to paramedics (e.g. physiotherapy), nor loss of productivity and costs and effects for relatives.

The appropriate technical devices for minimally invasive interventions in necrotizing pancreatitis have become more widely available and as a result clinical experience has increased worldwide. As a consequence, the answer to the question if there still is a place for a primary open necrosectomy in necrotizing pancreatitis becomes clearer. Following the randomized PANTER trial our group also performed the randomized TENSION trial to compare the endoscopic step-up approach with the surgical step-up approach and found no difference in major complications or death.[30] A recent international study pooled individual patient data of 1980 patients from 15 cohorts undergoing necrosectomy for necrotizing pancreatitis and found that minimally invasive necrosectomies (both

surgical and endoscopic) reduced in-hospital death in critically ill patients, as compared with open necrosectomy.[26] These findings are supported by recent large series.[25,31] Some advocate that a down-side of a minimally invasive step-up approach is that patients need additional invasive interventions during follow up because of persisting collections or necrosis and that for this reason a primary open necrosectomy is a more definitive initial treatment. Results of our current study refute this assumption and further accentuate the benefits of a minimally invasive step-up approach during follow up. It should be acknowledged, however, that necrotizing pancreatitis is a very heterogeneous disease. Different invasive treatment strategies therefore need to be considered in each individual patient, without ruling out the option of open necrosectomy. Nevertheless, following from the results of our longstanding experience in nationwide research on treatment of necrotizing pancreatitis, we feel confident to emphasize the long-term superiority of the minimally invasive step-up approach over primary open necrosectomy in the treatment of infected necrotizing pancreatitis.

**References**

1. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13:e1-15.

2. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology 2011;141:1254-1263.

3. Hollemans RA, van Brunschot S, Bakker OJ, et al. Minimally invasive intervention for infected necrosis in acute pancreatitis. Expert Rev Med Devices 2014;11:637-648.

4. van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med 2010;362:1491-1502.

5. Tenner S, Baillie J, DeWitt J, Vege SS, American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013;108:1400-1415.

6. Yokoe M, Takada T, Mayumi T, et al. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. J Hepatobiliary Pancreat Sci 2015;22:405-432.

7. Pezzilli R, Zerbi A, Campra D, et al. Italian Association for the Study of the Pancreas (AISP) Consensus guidelines on severe acute pancreatitis. Dig Liver Dis 2015;47:532-543.

8. Arvanitakis M, Dumonceau JM, Albert J, et al. Endoscopic management of acute necrotizing pancreatitis: European Society of GastrointestinalEndoscopy (ESGE) evidence-based multidisciplinary guidelines. Endoscopy 2018;50:524-546

9. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-343.

10. Ware JE,Jr. SF-36 health survey update. Spine 2000;25:3130-3139.

11. Schneider A, Lohr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. J Gastroenterol 2007;42:101-119.

12. Loser C, Mollgaard A, Folsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. Gut 1996;39:580-586.

13. Leeds JS, Oppong K, Sanders DS. The role of fecal elastase-1 in detecting exocrine pancreatic disease. Nat Rev Gastroenterol Hepatol 2011;8:405-415.

14. https://euroqol.org/ Accessed 10/09, 2017.

15. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055-1068.

16. Lamers LM, Stalmeier PF, McDonnell J, et al. Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff. Ned Tijdschr Geneeskd 2005;149:1574-1578.

17. Bloechle C, Izbicki JR, Knoefel WT, et al. Quality of life in chronic pancreatitis--results after duodenum-preserving resection of the head of the pancreas. Pancreas 1995;11:77-85.

18. https://www.nza.nl/regelgeving/formulieren/Aanleverformulier_NZa_kostprijsmodel_Medisch_specialistische_zorg_bij_NR_CU_261. Accessed 10/09, 2017.

19. https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg. Accessed 10/09, 2017.

20. Connor S, Alexakis N, Raraty MG, et al. Early and late complications after pancreatic necrosectomy. Surgery 2005;137:499-505.

21. Beck WC, Bhutani MS, Raju GS, et al. Surgical management of late sequelae in survivors of an episode of acute necrotizing pancreatitis. J Am Coll Surg 2012;214:682-688.

22. Das SL, Singh PP, Phillips AR, et al. Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis. Gut 2014;63:818-831.

23. Hollemans RA, Hallensleben NDL, Mager DJ, et al. Pancreatic exocrine insufficiency following acute pancreatitis: Systematic review and study level meta-analysis. Pancreatology 2018;18:253-263.

24. Cirocchi R, Trastulli S, Desiderio J, et al. Minimally invasive necrosectomy versus conventional surgery in the treatment of infected pancreatic necrosis: a systematic review and a meta-analysis of comparative studies. Surg Laparosc Endosc Percutan Tech 2013;23:8-20.

25. Gomatos IP, Halloran CM, Ghaneh P, et al. Outcomes From Minimal Access Retroperitoneal and Open Pancreatic Necrosectomy in 394 Patients With Necrotizing Pancreatitis. Ann Surg 2016;263:992-1001.

26. **van Brunschot S, Hollemans RA**, Bakker OJ, et al. Minimally invasive and endoscopic versus open necrosectomy for necrotising pancreatitis: a pooled analysis of individual data for 1980 patients. Gut 2018;67:697-706.

27. Wright SE, Lochan R, Imrie K, et al. Quality of life and functional outcome at 3, 6 and 12 months after acute necrotising pancreatitis. Intensive Care Med 2009;35:1974-1978.

28. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. Gastroenterology 2009;136:1134-1144.

29. Sprangers MA. Response-shift bias: a challenge to the assessment of patients' quality of life in cancer clinical trials. Cancer Treat Rev 1996;22 Suppl A:55-62.

30. van Brunschot S, van Grinsven J, van Santvoort HC, et al. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. Lancet 2018;391:51-58.

31. Rasch S, Phillip V, Reichel S, et al. Open Surgical versus Minimal Invasive Necrosectomy of the Pancreas-A Retrospective Multicenter Analysis of the German Pancreatitis Study Group. PLoS One 2016;11:e0163651.

32. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-111.

33. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care 2005;43:203-220.

Author names in bold designate shared co-first authorship.

**Figure 1** Patient flow chart

**Figure 2** Probabilities of primary endpoint free survival of patients randomized to the step-up approach and primary open necrosectomy.

**Table 1.** Clinical endpoints according to treatment group in 88 patients included in the PANTER trial.

| | Original follow-up period plus long-term follow up | | | | New events during long-term follow up | | | |
|---|---|---|---|---|---|---|---|---|
| **Outcome** | **Step-up approach (N = 43)** | **Open necrosectomy (N = 45)** | **Risk Ratio (95% CI)** | **P** | **Step-up approach (N = 35)** | **Open necrosectomy (N = 38)** | **Risk Ratio (95% CI)** | **P** |
| **Primary composite end point[#] - no. (%)** | 19 (44) | 33 (73) | 0.60 (0.41 - 0.88) | 0.005 | 5 (14) | 3 (8) | 1.81 (0.47 - 7.02) | 0.47* |
| **Secondary end points – no. (%)** | | | | | | | | |
| **New onset multiple organ failure or systemic complications** | 6 (14) | 19 (42) | 0.33 (0.15 - 0.75) | 0.003 | 1 (3) | 1 (3) | 1.09 (0.07 - 16.71) | 1.00* |
| **Multiple-organ failure** | 6 (14) | 18 (40) | 0.35 (0.15 - 0.80) | 0.006 | 1 (3) | 0 | - | 0.48* |
| **Multiple systemic complications** | 0 | 1 (2) | - | 1.00* | 0 | 0 | - | - |
| **Intraabdominal bleeding requiring intervention** | 7 (16) | 12 (27) | 0.61 (0.27 - 1.40) | 0.24 | 0 | 2 (5) | - | 0.49* |
| **Enterocutaneous fistula or perforation of a visceral organ requiring intervention** | 6 (14) | 10 (22) | 0.63 (0.25 - 1.58) | 0.32 | 0 | 0 | - | - |
| **Death** | 13 (30) | 9 (20) | 1.51 (0.72 - 3.17) | 0.27 | 5 (14) | 2 (5) | 2.71 (0.56 - 13.1) | 0.25* |
| **Other outcomes – no. (%)** | | | | | | | | |
| **Pancreatic fistula** | 12 (28) | 17 (38) | 0.74 (0.40 - 1.36) | 0.33 | 0 | 0 | - | - |
| **Incisional hernia[†]** | 10 (23) | 24 (53) | 0.44 (0.24 - 0.80) | 0.004 | 7 / 32 (20)[₸] | 13 / 26 (50)[₸] | 0.44 (0.20 - 0.93) | 0.03 |
| **New-onset endocrine insufficiency[¥]** | 17 (40) | 25 (56) | 0.74 (0.49 - 1.11) | 0.13 | 10 / 28 (36)[₸] | 8 / 21 (38)[₸] | 0.94 (0.45 - 1.96) | 0.61 |
| **New-onset pancreatic enzyme use** | 7 (16) | 19 (42) | 0.39 (0.18 - 0.82) | 0.006 | 4 / 32 (13)[₸] | 4 / 23 (17)[₸] | 0.72 (0.20 - 2.58) | 0.69 |

* The Chi square test was used unless indicated with an *, then the Fisher's exact test was used due to small numbers.
[#] Multiple events in the same patient were considered as 1 end point.
[¶] Mann-Whitney U test when median (range) and t-test for mean ± SD.
[†] Missing data: Incisional hernia new during follow-up years; 1 patient (open-necrosectomy group).
[¥] Defined as the use of oral antidiabetic and/ or insulin therapy.
[Ŧ] Patients who already developed an incisional hernia, endocrine insufficiency or exocrine insufficiency at the end of the PANTER trial (i.e. at the start of long-term follow up) were not included in the analysis.
[§] 2 distal pancreatectomies (indication: fistula, chronic pancreatitis), 1 pancreaticojejunostomy (indication fistula) and 2 marsupializations (indication chronic pancreatitis and residual symptomatic pancreatic fluid collection/ cyst).

**Table 2.** Outcome of step-up approach and open necrosectomy of survivors at long-term follow up.

| Outcome | Step-up approach (N = 30) | | Open necrosectomy (N = 36) | | P* |
|---|---|---|---|---|---|
| **Follow up (months)** | 85 ± 11 | | 87 ± 11 | | 0.45[#] |
| **Recurrent pancreatitis - no. (%)[Ŧ]** | 6 (20) | | 8 (22) | | 0.83 |
| **No. pancreatitis episodes per patient - median (range)[Ŧ]** | 3 (1 - 5) | | 1 (1 - 3) | | 0.09 |
| **New onset endocrine insufficiency - no. (%)** | | | | | |
| **Present at follow-up visit** | 12 (40) | | 23 (64) | | 0.053 |
| **Oral medication** | 8 (67) | | 20 (87) | | |
| **Insulin** | 5 (42) | | 14 (61) | | |
| **Exocrine insufficiency** | | | | | |
| **Fecal elastase-1 mean value[‡]** | 283 ± 141 | | 200 ± 150 | | 0.03[#] |
| **<200 µg / gram - no. (%)[‡]** | 8 / 28 (29) | | 18 / 32 (56) | | 0.03 |
| **Enzyme use at long-term follow up - no. (%)** | 5 (17) | | 14 (39) | | 0.047 |
| **Chronic pancreatitis - no. (%)** | 3 (10) | | 4 (11) | | 0.88 |
| | **Step-up approach (N = 28)[†]** | | **Open necrosectomy (N = 31)[†]** | | **P*** |
| **Abdominal complaints - no. (%)** | | | | | |
| **Bloating [‖]** | 8 (29) | 2 | 10 (32) | 8 | 0.76 |
| **Cramps [‖]** | 9 (32) | 3 | 10 (32) | 5 | 0.99 |
| **Diarrhea [‖]** | 4 (14) | 1 | 8 (26) | 3 | 0.27 |
| **Steatorrhea [‖]** | 5 (18) | 1 | 0 | - | 0.02* |
| **Izbicki pain score - mean ± SD** | 21 ± 27 | | 19 ± 25 | | 0.76[#] |
| **Patients with pain only** | N = 14 | 43 ± 23 | N = 14 | 42 ± 19 | 0.99[#] |

* The Chi square test was used unless indicated with an *, then the Fisher's exact test was used due to small numbers.
# Independent sample t-test for mean ± SD; Mann-Whitney U test for median (range).
Ŧ Defined by the Atlanta 2012 Classification.[32] Additional mild attacks for which patients were not admitted to the hospital are not accounted for.
‡ Fecal elastase-1 is measured in 60 patients; in 28 (93%) patients in the step-up group and 32 (89%) patients in the open-necrosectomy group. Fecal elastase-1 value is measured from 15-500 µg / gram. To patients with fecal elastase test levels of <15 µg / gram a value of 5 µg / gram was assigned and to patients with fecal elastase test levels of >500 µg / gram a value of 510 µg / gram was assigned.
† Izbicki pain score and abdominal complaints are scored for 28 patients in the step-up group and 31 patients in the open-necrosectomy group through outpatient visit and/or telephone interviews.
‖ The first column in each treatment group shows the number of patients with the symptom, the second column shows the number of patients who also have pancreatic exocrine insufficiency according to their fecal elastase-1 value. Statistical testing was performed on data in the first column.

| **Table 3.** Quality of life of 60 patients at long-term follow up after treatment for necrotizing pancreatitis.* | | | |
|---|---|---|---|
| | **Step-up approach (N = 28)** | **Open necrosectomy (N = 32)** | **P** |
| **SF-36 Physical health component** | | | |
| US standard | 43 ± 12 | 42 ± 11 | 0.63 |
| Dutch standard | 44 ± 12 | 43 ± 12 | 0.70 |
| **SF-36 Mental health component** | | | |
| US standard | 49 ± 11 | 50 ± 11 | 0.82 |
| Dutch standard | 47 ± 11 | 48 ± 11 | 0.89 |
| **EQ-5D based health utility scores** | | | |
| US values | 0.84 ± 0.17 | 0.78 ± 0.24 | 0.29 |
| Dutch values | 0.81 ± 0.21 | 0.75 ± 0.30 | 0.33 |
| **Health state score**[#] | 70 ± 19 | 69 ± 20 | 0.90 |

* Quality of life was scored for 28 patients in the step-up group and 32 patients in the open-necrosectomy group through validated, patient reported questionnaires. The scores on the SF-36 physical and mental health components range from 0 to 100, with higher scores indicating better quality of life. Linear transformations were performed to standardize the scores to a mean score of 50 ± 10 in a general US and Dutch population. The utilities of the observed health score profiles on the EQ-5D are based on the time trade-off elicitation technique from interviews with adults from the US general population and the Dutch general population, respectively.[16,33] Utilities range from either -0.109 (US) or - 0.330 (Dutch), indicating serious health problems, to 1.0, indicating no problems at all.

[#]The Health state scores range from 0 to 100, with higher scores indicating better perceived health.

**Table 4.** Health care resource utilization according to treatment group in 88 patients included in the PANTER trial.

| | Original follow-up period plus long-term follow up | | | | New events during long-term follow up | | | |
|---|---|---|---|---|---|---|---|---|
| **Outcome** | **Step-up approach (N = 43)** | **Open necrosectomy (N = 45)** | **Risk Ratio (95% CI)** | **P** | **Step-up approach (N = 35)** | **Open necrosectomy (N = 38)** | **Risk Ratio (95% CI)** | **P** |
| **Catheter drainage of peripancreatic fluid collection - no. (%)** | 43 (100) | 21 (47) | - | <0.001 | 4 (11) | 5 (13) | 0.87 (0.25 - 2.98) | 1.00* |
| **No. of drainage procedures** | 87 | 40 | | | 5 | 8 | | |
| **Necrosectomy of pancreatic necrosis - no. (%)** | 26 (60) | 45 (100) | - | <0.001 | 0 | 0 | - | - |
| **Other pancreatic surgery**[#] | 4 (11) | 2 (5) | - | - | 4 (11) | 2 (5) | 2.17 0.42 - 11.13) | 0.42* |
| **Incisional hernia repair** | 6 (17) | 12 (32) | - | - | 6 (17) | 12 (32) | 0.54 (0.23 - 1.29) | 0.15 |
| **Ileostomy / colostomy reversal** | 2 (5) | 5 (11) | 0.42 (0.09 - 2.04) | 0.13 | 2 (6) | 3 (8) | 0.72 (0.13 - 4.08) | 0.71 |
| **Cholecystectomy** | 18 (42) | 22 (49) | 0.86 (0.54 - 1.36) | 0.51 | 9 (26) | 8 (21) | 1.22 (0.53 - 2.81) | 0.64 |
| **Days in hospital - median (range)** | 72 (1 - 287) | 73 (1 - 297) | - | 0.74 | 9 (0 - 230) | 17 (0 - 113) | - | 0.42 |
| **Related to necrotizing pancreatitis** | - | - | - | - | 0 (0 - 112) | 8 (0 - 51) | - | 0.27 |
| **Unrelated to necrotizing pancreatitis** | - | - | - | - | 3 (0 - 118) | 5 (0 - 108) | - | 0.71 |
| **Days in intensive care unit - median (range)** | 13 (0 - 281) | 11 (0 - 111) | - | 0.33 | 0 (0 - 29) | 0 (0 - 12) | - | 0.28 |
| **Related to necrotizing pancreatitis** | - | - | - | - | 0 (0 - 2) | 0 (0 - 9) | - | 0.78 |
| **Unrelated to necrotizing pancreatitis** | - | - | - | - | 0 (0 - 29) | 0 (0 - 12) | - | 0.08 |

* The Chi square test was used unless indicated with an *, then the Fisher's exact test was used due to small numbers.

[#] 2 distal pancreatectomies (indication: fistula, chronic pancreatitis), 2 pancreaticojejunostomies (indication fistula) and 2 marsupializations (indication chronic pancreatitis and residual symptomatic pancreatic fluid collection / cyst).