# Acute pancreatitis: from treatment to prevention

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# PART I

Treatment of infected necrotizing pancreatitis

# CHAPTER 2

## Long-term outcome of immediate versus postponed intervention in patients with infected necrotizing pancreatitis (POINTER): *multicenter randomized trial*

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## ABSTRACT

**Objective:** To compare the long-term outcomes of immediate drainage versus the postponed-drainage approach in patients with infected necrotizing pancreatitis.

**Background:** In the randomized POINTER trial, patients assigned to the postponed-drainage approach using antibiotic treatment required fewer interventions, as compared with immediate drainage, and over a third were treated without any intervention.

**Methods:** Clinical data of those patients alive after the initial 6-month follow-up were re-evaluated. The primary outcome was a composite of death and major complications.

**Results:** Out of 104 patients, 88 were re-evaluated with a median follow-up of 51 months. After the initial 6-month follow-up, the primary outcome occurred in 7 of 47 patients (15%) in the immediate-drainage group and 7 of 41 patients (17%) in the postponed-drainage group (RR 0.87, 95% CI 0.33-2.28; p=0.78). Additional drainage procedures were performed in 7 patients (15%) versus 3 patients (7%) (RR 2.03; 95% CI 0.56-7.37; p=0.34). The median number of additional interventions was 0 (IQR 0-0) in both groups (p=0.028). In the total follow-up, the median number of interventions was higher in the immediate-drainage group than in the postponed-drainage group (4 vs 1, p=0.001). Eventually, 14 of 15 patients (93%) in the postponed-drainage group who were successfully treated in the initial 6-month follow-up with antibiotics and without any intervention, remained without intervention. At the end of follow-up, pancreatic function and quality of life were similar.

**Conclusions:** Also, during long-term follow-up, a postponed drainage approach using antibiotics in patients with infected necrotizing pancreatitis results in fewer interventions as compared with immediate drainage and should therefore be the preferred approach.

# INTRODUCTION

Acute pancreatitis mostly runs a mild clinical course, but 20% of patients develop severe pancreatitis with necrosis (1-4). Secondary infection of pancreatic and peripancreatic necrosis puts these patients at risk of significant morbidity and 10% to 39% mortality (5). Several randomized studies have attempted to optimize the treatment of patients with infected necrotizing pancreatitis (6-11). Besides antibiotic treatment, the minimally invasive step-up approach, with catheter drainage of the infected necrotic collection as the first step followed by minimally invasive necrosectomy when needed, is the current standard treatment strategy. However, the optimal timing of drainage in infected necrotizing pancreatitis remains unknown and varies widely in current practice (12-14).

The recent multicenter randomized POINTER trial compared immediate catheter drainage within 24 hours after diagnosing infected pancreatic necrosis, with postponed catheter drainage (11). At 6-month follow-up, immediate drainage was not superior to postponed drainage regarding complications. In fact, the postponed-drainage approach significantly reduced the number of invasive interventions, both catheter drainage and necrosectomy. Some 19 patients (39%) assigned to the postponed-drainage group did not require any intervention because their clinical condition improved with antibiotic treatment only; 17 of these patients (35%) survived. The question remains whether these relative benefits of the postponed-drainage approach persist after the initial 6-month follow-up. Some have argued that infected (peri)pancreatic necrotic collections, which are initially treated conservatively with antibiotics could lead to persistent complications requiring intervention and ultimately causing mortality during longer follow-up.

Therefore, the current study evaluates new events beyond the initial 6-month follow-up on long-term clinical outcomes of patients enrolled in the POINTER trial.

# METHODS

## Study design

Between August 2015 and October 2019, a total of 104 patients with infected necrotizing pancreatitis were enrolled in the multicenter randomized POINTER (Postponed or Immediate Drainage of Infected Necrotizing Pancreatitis) trial (11, 15). The study was conducted in 22 Dutch hospitals collaborating with the Dutch Pancreatitis Study Group (DPSG). Infected necrosis was defined as either a positive fine-needle aspiration (FNA) culture, presence of gas in (peri)pancreatic necrosis on contrast-enhanced

computed tomography, and after 14 days of onset, clinical signs of infection were also considered to be diagnostic if other causes of infections were ruled out. Clinical signs of infection were defined as: persistent (multiple) organ failure, or the presence of 2 of 3 elevated inflammatory parameters (temperature >38.5, C-reactive protein levels or leukocyte count) for three consecutive days. Patients were randomly assigned to immediate catheter drainage (55 patients) or postponed catheter drainage (49 patients). The study protocol of the current investigator-initiated long-term follow-up study was approved by the institutional review board of the Amsterdam UMC. All authors had access to the study data, and reviewed and approved the final version of the manuscript. The study was conducted in accordance with the principles of the Declaration of Helsinki and reported according to the STROBE Checklist (Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/ SLA/E733) (16).

## Long-term follow-up protocol

Surviving patients from the POINTER trial were informed about the study by telephone and subsequently invited to participate. Written informed consent was obtained from all patients with the exception of deceased patients. Eligible patients were evaluated until June 2022, following the initial POINTER study which had a 6-month follow-up. Clinical data regarding death, complications, interventions (i.e. drainage and necrosectomy procedures), readmission and disease course was retrieved retrospectively from medical records. Interventional procedures related to disconnected pancreatic duct syndrome were also recorded. Additional data were collected by a telephone conversation with patients or family members by the study coordinators (C.v.V. and N.S.). The choice of treatment (i.e., type and timing of interventions) was left to the treating physician and no particular criteria were formulated to guide the decisions of the physicians. For data collection, online database software (Castor EDC, Amsterdam, the Netherlands) was used.

## Outcomes

The primary outcome was a composite of death and major complications (i.e., new-onset (multiple) organ failure, bleeding requiring intervention, perforation of a visceral organ requiring intervention or enterocutaneous fistula, similar to other trials and follow-up studies performed by our group (6, 17). This primary outcome differed from the original primary outcome (i.e. Comprehensive Complication Index [CCI]), because CCI would be less relevant during follow-up, because this tool was developed to assess short-term complications (18-20). The primary outcome was selected based on the hypothesis that residual (peri)pancreatic necrotic collections, especially in the postponed treatment group, could require new interventions and ultimately cause mortality during longer follow-up. In accordance with the initial study, secondary outcomes included individual major complications, incisional hernia, pancreaticocutaenous fistula, wound infection,

interventions, the total length of intensive care and hospital stay related to pancreatitis length. In addition, the occurrence of recurrent acute pancreatitis and chronic pancreatitis was assessed. Furthermore, we evaluated exocrine and endocrine pancreatic function based on a questionnaire, and quality of life measured with the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) (21). Outcomes were assessed for the period after the trial's initial 6-month follow-up until the end of long-term follow-up *('new events after the initial 6-month follow-up'*) for all patients who were still alive after the initial 6-month follow-up. Separately, all events between the time of randomization and the end of long-term follow-up ('*total follow-up')* were reported for all patients, including patients who died in the initial 6-month follow-up, with the exception of patients who declined to participate in this follow-up study. This will provide a complete overview and accurate comparison between the 2 different treatment groups.

**Definitions**

All definitions were according to the initial POINTER trial and are explained in detail in the Supplementary Table S2 (Supplemental Digital Content 1, http://links.lww.com/SLA/E733). Patients were considered to have endocrine pancreatic insufficiency in case of use of diabetes medication (i.e. oral medication or insulin therapy), not used at the time of randomization. Exocrine pancreatic insufficiency was defined as the use of pancreatic enzymes, not used at the time of randomization. We considered successful treatment with antibiotics only if patients survived the initial 6-month follow-up and were treated without any intervention during total follow-up. The diagnosis of disconnected duct was based either on radiological confirmation or on an amylase level in external drain fluid of 3 times the upper limit of normal amylase level The follow-up period was defined as the time between randomization and the date of data entry in surviving patients or the date of death in deceased patients.

**Statistical analysis**

The analysis was performed according to the intention-to-treat principle. Outcome measures are expressed as means ± standard deviation (SD) or as medians with interquartile ranges (IQR), depending on the distributional properties. Categorical data are presented as counts and proportions. For normally distributed continuous data, statistical significance was assessed using the Student's-*t*-test. For non-normally distributed continuous data, the Mann-Whitney U test was performed. For categorical data, the Fisher's exact test was performed. Sensitivity analyses excluding patients in whom the diagnosis was based on FNA and radiographic appearance were performed. Results are expressed as relative risks (RRs) with corresponding 95% confidence intervals (CI). All reported *P* values are two-sided, and a *P* value of less than 0.05 was considered statistically significant. *P* values were not adjusted for multiple testing. All statistical analyses were conducted with IBM Statistic SPSS 26.0.

## RESULTS

Overall, 104 patients with infected necrotizing pancreatitis were randomized in the initial POINTER trial. As shown in Fig 1, 12 of 104 patients died during the initial 6-month follow-up; 7 patients in the immediate-drainage group versus 5 patients in the postponed-drainage group. Of the 92 surviving patients, 4 patients (who were all still alive) did not consent to participate in the current long-term follow-up study, leaving 88 patients (47 patients in the immediate-drainage group and 41 patients in the postponed-drainage group) to be included in the analysis 'new events after the initial 6-month follow-up'. These 88 patients, together with the 12 patients who died in the initial 6-month follow-up, were included in the 'total follow-up' analysis, resulting in a total of 100 patients (54 in the immediate-drainage group and 46 in the postponed-drainage group). At the end of the long-term follow-up, questionnaires were obtained from 79 patients (42 patients in the immediate-drainage group and 37 patients in the postponed-drainage group). Baseline characteristics were similar between the 2 groups (Supplementary Table S3, Supplemental Digital Content 1, http://links.lww.com/SLA/E733) (11). The total follow-up was 51 months (IQR 31) (50 months (IQR 32) in the immediate-drainage group and 51 months (IQR 29) in the postponed-drainage group), and did not statistically differ among groups (p=0·91).

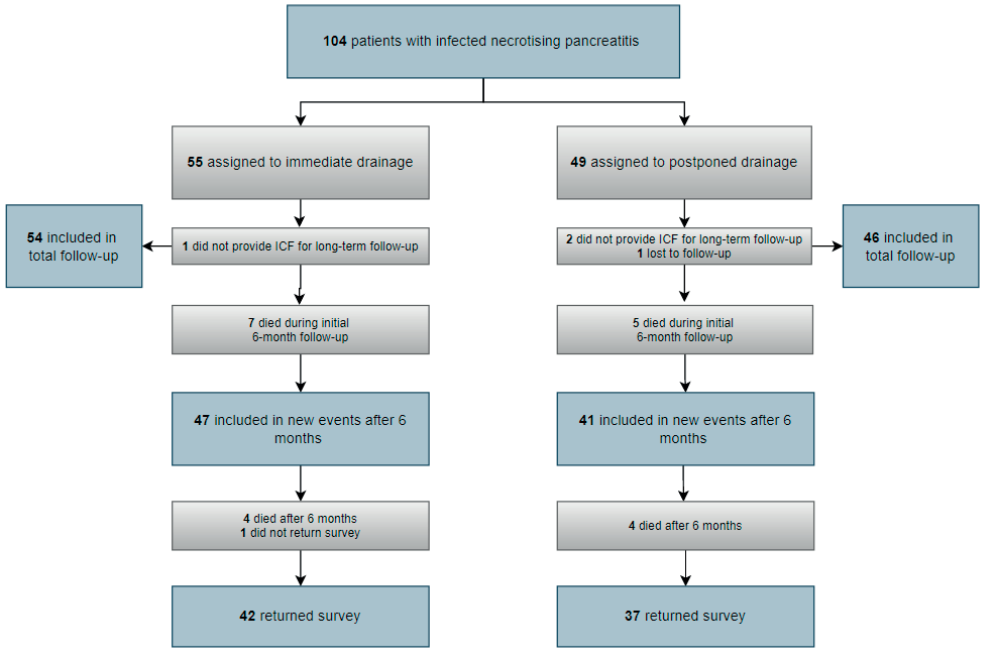


**Figure 1.** Trial profile

**New events after the initial 6-month follow-up**

After the initial 6-month follow-up, the composite primary outcome of death and major complications occurred in 7/47 patients (15%) in the immediate-drainage group and 7/41 patients (17%) in the postponed-drainage group (RR 0·87; 95% CI 0·33-2·28; p=0·78) (Table 1). Death occurred in 4 patients in the immediate-drainage group (9%) and in 4 patients in the postponed-drainage group (10%), (RR 0·87; 95% CI 0·23-3·27; p=1·00). Two deaths in the immediate-drainage group were directly related to pancreatitis, whereas none of the deaths in the postponed-drainage group (Supplementary Table S4, Supplemental Digital Content 1, http://links.lww.com/SLA/E733). No significant differences were found in the individual components of major complications, including new-onset organ failure (9% in the immediate-drainage group and 5% in the postponed-drainage group; RR 1·75; 95% CI 0·34-9·04; p=0·68), multiple new-onset organ failure (2% and 0%, respectively; p=1·00), bleeding (2% and 0%, respectively; p=1·00), perforation of a visceral organ or enterocutaneous fistula (2% and 2%, respectively; RR 0·87; 95% CI 0·06-13·51; p=1·00). The incidence of other outcomes, including incisional hernia (4% and 2%, respectively; RR 2·86; 95% CI 0·32-25·72; p=0·54), pancreaticocutaenous fistula (2% and 0%, respectively; p=1·00), and wound infection (2% and 5%, respectively; RR 0·44; 95% CI 0·04-4·64; p=0·60), did not differ significantly.

Recurrent acute pancreatitis and chronic pancreatitis occurred in 7 patients (15%) and 5 patients (11%) in the immediate-drainage group versus 5 patients (12%) and 2 patients (5%) in the postponed-drainage group (RR 1·53; 95% 0·48-4·85; p=0·47; RR 2·18; 95% 0·45-10·6; p=0·44), respectively.

One or more drainage procedures were required in 7 patients (15%) in the immediate-drainage group versus 3 patients (7%) in the postponed drainage group (RR 2·03; 95% CI 0·56-7·37; p=0·33) after the initial 6-month follow-up; of which one was initially treated with antibiotics alone. Signs of a disrupted or disconnected pancreatic duct were present in 3 of those patients (30%). No patient in both groups needed a necrosectomy after the initial 6-month follow-up. The median number of drainage procedures and necrosectomies was 0 [IQR 0] in both groups (p=0·28). More details regarding interventions are given in Supplementary Table S5, Supplemental Digital Content 1, http://links.lww.com/SLA/ E733. The median length of intensive care stay was 0 days [IQR 0] in both groups (p=0·69), and hospital stay was 0 days [IQR 16] in the immediate-drainage group and 2 [IQR 5] in the postponed-drainage group (p=0·09), respectively. Results of the sensitivity analyses are provided in Supplementary Table S6, Supplemental Digital Content 1, http://links.lww.com/SLA/ E733.

**Table 1.** Primary and secondary outcomes[a]

| | **New events after the initial 6-month follow-up** (excluding events as initially reported in the POINTER trial) | | | | **Total follow-up[b]** (time between randomization and the end of long-term follow-up) | | | |
|---|---|---|---|---|---|---|---|---|
| **Outcome** | **Immediate Drainage (*n* = 47)** | **Postponed Drainage (*n* = 41)** | **Relative risk (95% CI)** | **P-value** | **Immediate Drainage (*n* = 54)** | **Postponed Drainage (*n* = 46)** | **Relative risk (95% CI)** | **P-value** |
| **Primary outcomes – no. (%)** | | | | | | | | |
| Major complications or death | 7 (15) | 7 (17) | 0.87 (0.33-2.28) | 0.78 | 26 (48) | 21 (46) | 1.06 (0.69-1.60) | 0.80 |
| Secondary outcomes – no. (%)[c] | | | | | | | | |
| Death | 4 (9) | 4 (10) | 0.87 (0.23-3.27) | 1.00 | 11 (20) | 9 (20) | 1.04 (0.47-2.29) | 0.92 |
| New-onset organ failure | 4 (9) | 2 (5) | 1.75 (0.34-9.04) | 0.68 | 17 (31) | 12 (26) | 1.21 (0.65-2.26) | 0.55 |
| - Pulmonary | 3 (6) | 2 (5) | 1.31 (0.23-7.45) | 1.00 | 8 (15) | 10 (22) | 0.68 (0.29-1.58) | 0.37 |
| - Cardiovascular | 3 (6) | 1 (2) | 2.62 (0.28-24.19) | 0.62 | 13 (24) | 10 (22) | 1.11 (0.54-2.29) | 0.78 |
| - Renal | 0 | 0 | - | - | 3 (6) | 4 (9) | 0.64 (0.15-2.71) | 0.70 |
| Multiple new-onset organ failure | 1 (2) | 0 | - | 1.00 | 5 (9) | 8 (17) | 0.53 (0.19-1.52) | 0.23 |
| Bleeding requiring intervention | 1 (2) | 0 | - | 1.00 | 8 (15) | 10 (22) | 0.68 (0.29-1.58) | 0.37 |
| Perforation of a visceral organ or enterocutaneous fistula | 1 (2) | 1 (2) | 0.87 (0.06-13.51) | 1.00 | 5 (9) | 5 (11) | 0.85 (0.26-2.76) | 1.00 |
| **Other outcomes – no. (%)** | | | | | | | | |
| Incisional hernia | 2 (4) | 1 (2) | 2.86 (0.32-25.72) | 0.54 | 2 (4) | 1 (2) | 1.70 (0.16-18.2) | 1.00 |
| Pancreaticocutaneous fistula | 1 (2) | 0 | - | 1.00 | 7 (13) | 4 (9) | 1.49 (0.47-4.77) | 0.50 |
| Wound infection | 1 (2) | 2 (5) | 0.44 (0.04-4.64) | 0.60 | 1 (2) | 3 (7) | 0.28 (0.03-2.64) | 0.33 |
| Recurrent acute pancreatitis | 7 (15) | 5 (10) | 1.53 (0.48-4.85) | 0.47 | n.a. | n.a. | n.a. | n.a. |
| Chronic pancreatitis | 5 (12) | 2 (5) | 2.18 (0.45-10.6) | 0.44 | n.a. | n.a. | n.a. | n.a. |

*Data are presented as no. (%). [a]Multiple events in the same patient were scored as one outcome. [b]4 patients (of the originally 104 included patients) from the POINTER trial did not consent to participate in this follow-up study and were therefore missing in the total follow-up analysis. [c]Individual components of the composite primary outcome.*

### Total follow-up

In the total follow-up, the composite primary outcome of death and major complications occurred in 26/54 patients (48%) in the immediate-drainage group and in 21/46 patients (46%) in the postponed-drainage group (RR 1·06; 95% CI 0·69-1·60; p=0·80) (Table 1). Death occurred in 11 patients (20%) and 9 patients (20%) in the immediate-drainage group and postponed-drainage group, respectively. No differences were found in the individual components of major complications.

All 54 patients (100%) in the immediate-drainage group underwent catheter drainage in the total follow-up, whereas 30 patients (65%) in the postponed-drainage group (RR 1·53; 95% CI 1·24-1·89; p<0·0001) (Table 2). Necrosectomy was performed in 28 patients (52%) in the immediate-drainage group versus 11 patients (24%) in the postponed-drainage group (RR 2.17; 95% CI 1.22-3.86; p=0·001). Patients in the postponed-drainage group required fewer catheter drainages (1 [IQR 3] versus 3 [IQR 4]; p=0·00) and necrosectomies (1 [IQR 1] versus 2 [IQR 1]; p=0·01) compared with patients in the immediate-drainage group. The median number of surgical, endoscopic and radiologic interventions (catheter drainage and necrosectomy) was 4 [IRQ 5] in the immediate-drainage group versus 1 [IQR 6] in the postponed-drainage group (p=0.001).

### Patients successfully treated with antibiotics only

Of the 17 patients in the postponed drainage group who survived the initial 6-month follow-up and were successfully treated with antibiotics only, for example, without any interventions, 2 patients did not provide informed consent to this study, leaving 15 patients to be included in these analyses. Of these patients, 14 patients (93%) remained without intervention at the end of long-term follow-up. Ultimately, 14 out of 44 patients (35%) assigned to the postponed-drainage group were successfully treated with antibiotics only in the total follow-up.

### End of long-term follow-up

At the end of long-term follow-up, there were no differences in the new development of exocrine and endocrine pancreatic insufficiency (Table 3). The exocrine and endocrine pancreatic function over time is presented in Supplementary Table S7, Supplemental Digital Content 1, http://links.lww.com/SLA/ E733. The quality of life scores, SF-36 physical and mental health scores, at the end of long-term follow-up were also comparable among groups; the physical component scale was 49 (±14) and 43 (±22) (p=0·17) whereas the mental component scale was 43 (±8) and 42 (±9) (p=0·43) in the immediate- and postponed-drainage group, respectively.

**Table 2.** Interventions and health care utilization[a]

| | **New events after the initial 6-month follow-up** (excluding events as initially reported in the POINTER trial) | | | | **Total follow-up**[b] (time between randomization and the end of long-term follow-up) | | | |
|---|---|---|---|---|---|---|---|---|
| **Outcome** | **Immediate Drainage (*n* = 47)** | **Postponed Drainage (*n* = 41)** | **Relative risk (95% CI)** | **P-value** | **Immediate Drainage (*n* = 54)** | **Postponed Drainage (*n* = 46)** | **Relative risk (95% CI)** | **P-value** |
| Catheter Drainage – no. (%) | 7 (15) | 3 (7) | 2.03 (0.56-7.37) | 0.33 | 54 (100) | 30 (65) | 1.53 (1.24-1.89) | 0.000 |
| Necrosectomy – no. (%) | 0 | 0 | - | - | 28 (52) | 11 (24) | 2.17 (1.22-3.86) | 0.004 |
| Median total surgical, endoscopic, and radiologic interventions for infected necrosis (IQR) – no. | 0 (0-0) | 0 (0-0) | - | 0.28 | 4 (2-7) | 1 (0-6) | - | 0.001 |
| Median total drainage procedures (IQR) - no. | 0 (0-0) | 0 (0-0) | - | 0.28 | 3 (1-5) | 1 (0-3) | - | 0.000 |
| No. of drainage procedures (%) – no. of patients (%) | | | | | | | | |
| 0 | 40 (85) | 38 (93) | - | - | 0 | 16 (35) | - | - |
| 1 | 6 (13) | 2 (5) | - | - | 19 (35) | 16 (35) | - | - |
| 2 | 0 | 0 | - | - | 6 (11) | 0 | - | - |
| ≥3 | 1 (2) | 1 (2) | - | - | 29 (54) | 14 (30) | - | - |
| Median total necrosectomies (IQR) – no. | 0 (0-0) | 0 (0-0) | - | - | 1 (0-1) | 0 (0-0) | - | 0.01 |
| No. of necrosectomies – no. of patients (%) | | | | | | | | |
| 0 | 47 (100) | 41 (100) | - | - | 27 (50) | 38 (82) | - | - |
| 1 | 0 | 0 | - | - | 13 (24) | 4 (9) | - | - |
| 2 | 0 | 0 | - | - | 3 (6) | 1 (3) | - | - |
| ≥3 | 0 | 0 | - | - | 12 (22) | 6 (13) | - | - |
| Median length of stay in ICU (IQR) – days | 0 (0-0) | 0 (0-0) | - | 0.69 | 0 (0-16) | 0 (0-10) | - | 0.80 |
| Median length of stay in hospital (IQR) – days related to pancreatitis | 0 (0-16) | 2 (0-5) | - | 0.56 | 57 (37-90) | 41 (22-76) | - | 0.09 |

*Data are presented as no. (%) or median (IQR). [a]Multiple events in the same patient were scored as one outcome. [b]4 patients (of the originally 104 included patients) from the POINTER trial did not consent to participate in this follow-up study and were therefore missing in the total follow-up analysis. ICU = intensive care unit.*

**Table 3.** Pancreatic function and quality of life at the end of long-term follow-up[a]

| Outcome | Immediate Drainage (*n* = 42) | Postponed Drainage (*n* = 37) | Relative risk (95% CI) | P-value |
|---|---|---|---|---|
| Exocrine pancreatic insufficiency | | | | |
| Enzyme supplement use | 18 (43) | 13 (35) | 1.22 (0.70-2.13) | 0.48 |
| Endocrine pancreatic insufficiency | 18 (43) | 13 (35) | 1.22 (0.70-2.13) | 0.48 |
| Oral antidiabetics use only | 5 (12) | 2 (5) | 2.20 (0.45-10.68) | 0.44 |
| Insulin use only | 8 (19) | 10 (27) | 0.71 (0.31-1.60) | 0.40 |
| Oral antidiabetics and insulin use | 5 (12) | 1 (3) | 4.41 (0.54-36.01) | 0.21 |
| Quality of Life (SF-36) | | | | |
| PCS | 49 (14) | 43 (22) | - | 0.17 |
| MCS | 43 (8) | 42 (9) | - | 0.43 |

*Data are presented as no. (%) or mean (SD). [a]At the end of long-term follow-up, data from questionnaires were obtained from all but one surviving patients (n=79). PCS = Physical Component Scale. MCS = Mental Component Scale. The scores of both PCS and MCS range from 0 to 100, with higher scores indicating better quality of life.*

## DISCUSSION

This long-term follow-up study of the POINTER trial confirms that a postponed-drainage approach for infected necrotizing pancreatitis resulted in fewer interventions, as compared with immediate drainage, and almost a third of these patients were successfully treated with antibiotics only. Postponing or even omitting drainage does not lead to long-term adverse outcomes in patients with infected necrotizing pancreatitis.

In line with previous studies, no benefits of immediate drainage in comparison with delaying intervention were seen (12, 22-25). Nevertheless, one may argue that a subset of patients still benefit from an immediate approach, as in general the duration of organ failure impacts clinical outcomes (26). A recent pilot randomized controlled trial evaluated the optimal timing of percutaneous drainage in necrotizing pancreatitis with persistent organ failure as the primary indication and reported a beneficial trend for early drainage (27). But, the long-term outcomes of both approaches are only evaluated by 1 small non-randomized study, wherein no difference in regression and recurrence of collections were observed (25).

The most remarkable benefit of a postponed-drainage approach found in the initial POINTER trial was that 39% of patients assigned to the postponed-drainage group were treated with antibiotics alone (i.e. no catheter drainage or other intervention), with 35% of patients surviving the trials' initial 6-month follow-up (11). In the

current long-term follow-up study, this benefit continued in 93% of the surviving patients as the intervention was required in 1 initially conservatively treated patient. It is noteworthy that this patient declined cholecystectomy following the initial episode of acute biliary pancreatitis and subsequently developed recurrent acute pancreatitis with infected pancreatic necrosis.

In the total follow-up period, 35% of patients were successfully treated with antibiotics only. It should be pointed out here that the majority of patients did not suffer from (multiple) organ failure at randomization (Supplementary Table S2, Supplemental Digital Content 1, http://links.lww.com/SLA/ E733). This is in line with previous studies that have reported similar success rates of antibiotic treatment (range 3% to 39%) in selected patients with infected necrotizing pancreatitis, mostly in patients without organ failure. Future studies will have to confirm the optimal selection criteria for antibiotic treatment, in which procalcitonin should be considered (28), and determine details of treatment, including aspects of antibiotic stewardship. A prediction model selecting patients for an antibiotics-only-approach would be useful and should be developed.

As the results of this study will further enhance the use of antibiotic treatment, efforts to optimize the quality of its use should be made (29). A recent Dutch study evaluated antibiotic use and obtained pancreatic cultures of patients with infected necrotizing pancreatitis, and found that 48% received inappropriate empirical broad-spectrum antibiotics based on the identified microorganisms (30). Another concern about antibiotic (over)use, which in turn has a great impact on antibiotic resistance, is that antibiotics are often not tailored to (FNA-)culture results. Furthermore, the optimal treatment duration for infected necrosis is unknown. We hypothesize that an antibiotic stewardship-driven approach, which includes recommendations on FNA, and the timing and duration of antibiotic treatment, will result in similar patient outcomes and health care use, as compared with current practice.

During the present long-term follow-up, after the initial 6-month period, necrosectomy was not performed in any patient, meaning that 51% of patients in the immediate-drainage group and 22% of patients in the postponed-drainage group underwent necrosectomy ($p=0.004$) in the total follow-up. This is lower than the 51% to 60% rates of necrosectomy previously reported in patients with infected necrotizing pancreatitis treated with the step-up approach (17, 31). However, also both these studies stated a negligibly low need for additional necrosectomy after the 6-month follow-up. Another long-term benefit of postponed drainage includes the decreased need for drainage procedures and necrosectomy. The question remains whether postponing drainage through encapsulation of the necrotic collection, actually enables

a more effective drainage procedure, thereby making multiple procedures and even necrosectomy redundant (32).

At the end of long-term follow-up, pancreatic function (i.e. exocrine and endocrine) did not differ between the 2 groups. Both exocrine and endocrine insufficiency were present in 43% of patients in the immediate-drainage group and 35% in the postponed-drainage group. Previous literature that evaluated late-onset exocrine insufficiency showed similar prevalence rates (17, 31, 33), underlining the importance of monitoring exocrine pancreatic function over time. In our study, the fecal elastase-1 test was only performed in 61% of patients during long-term follow-up. Moreover, we showed that 22% of patients developed endocrine pancreatic insufficiency after the initial 6-month follow-up. It remains unclear, however, how this should be interpreted, since we cannot clearly differentiate between post-pancreatitis diabetes and the occurrence of new-onset type 2 diabetes (34). Quality of life was similar in both groups. Other long-term follow-up studies in necrotizing pancreatitis patients showed similar quality of life scores, wherein the hypothesis is that over the years, patients adapt to their morbidity and thereby the quality of life improves when compared with the baseline (17, 35, 36)

There are several limitations that need to be taken into account when interpreting the results of this study. First, the sample size was relatively small, although this study represents the largest follow-up study evaluating both approaches. Second, the long-term follow-up period was not standardized. As a result, the duration of follow-up differed between the first and last randomized patient, ranging from 7 years to 2.5 years, respectively. However, in the postponed-drainage group, all first drainage procedures after the initial 6-month follow-up were performed in the first 2 years after randomization with the exception of one (Supplementary Table S5, Supplemental Digital Content 1, http://links.lww.com/SLA/ E733). In addition, the total follow-up time did not differ between treatment groups. Third, the decision to intervene after the initial 6-month follow-up was not standardized. Nonetheless, the DPSG utilizes a nationwide expert panel (37), which helps minimize treatment variation and inequivalent access to specialized care. In cases where the patient showed no improvements with antibiotics, our experts recommended catheter drainage. If drainage had already been performed, further steps such as a new computed tomography scan and potential drain revision/upgrade, or necrosectomy, were advised. Fourth, some data (e.g. complications, intervention, hospital stay) were collected retrospectively which may have led to information bias. Fifth, endocrine and exocrine pancreatic function were pragmatically evaluated based on the use of medication and therefore, do not always reflect the accurate status of pancreatic insufficiency. The main strength is the

long-term follow-up of the multicenter randomized POINTER trial in a cohort of patients with infected necrotizing pancreatitis.

## CONCLUSION

Postponed catheter drainage, using antibiotics, may be seen as the preferred approach when treating patients with infected necrotizing pancreatitis. Delaying drainage reduces the number of interventions and offers the opportunity to effectively treat patients with antibiotic treatment only without increased risk for adverse long-term outcomes. The decision to postpone intervention, however, should be individualized and based on the patient's clinical course and improvement on antibiotics. Further research in this field, including the exact role of antibiotics in the management of infected necrosis, is encouraged.

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**Supplementary table S1**. STROBE checklist

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Page 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Page 3 |
| **Introduction** | | | |
| Background/ rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Page 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Page 4 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | Page 5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Page 5 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | Page 5 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Page 6-7 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Page 6-7 |
| Bias | 9 | Describe any efforts to address potential sources of bias | N.A. |
| Study size | 10 | Explain how the study size was arrived at | N.A. |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Page 7-8 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Page 7-8 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed | Page 9 / Figure 1 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |

**Supplementary table S1**. STROBE checklist (*continued*)

| | Item No | Recommendation | Page No |
|---|---|---|---|
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Supplementary Table S3 |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| | | (c) Summarise follow-up time (eg, average and total amount) | |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | Page 9-11 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Page 9-11 |
| | | (*b*) Report category boundaries when continuous variables were categorized | N.A. |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | N.A. |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | Page 10-11 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Page 13 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Page 15-16 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Page 13-16 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | Page 13-16 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Page 8 |

**Give information separately for exposed and unexposed groups. Information on the STROBE Initiative is available at http://www.strobe-statement.org.*

**Supplementary table S2**. Definitions of the primary and secondary outcomes

| Outcome | Definition |
|---|---|
| Primary outcome | The primary outcome was a composite of death and major complications. |
| Secondary outcomes | |
| • Major complications | |
| New onset organ failure | Organ failure occurring after randomization and not present 24 hours before randomization:<br>- Pulmonary: a PaO2 < 60 mmHg despite FiO2 30% or the need for mechanical ventilation<br>- Cardiovascular: a systolic blood pressure < 90 mmHg despite adequate fluid resuscitation or need for vasopressor support<br>- Renal: a serum creatinine > 177 mmol/L after rehydration or need for hemofiltration or hemodialysis (in case patients already suffered from renal insufficiency before this episode of AP [creatinine > 177 umol/L] this does not count as renal failure) |
| Multiple organ failure | Failure of 2 or more organ systems (i.e. respiratory, cardiovascular or renal) at the same moment. |
| Bleeding requiring intervention | Bleeding requiring surgical, radiologic, or endoscopic intervention. |
| Perforation of a visceral organ requiring intervention | Perforation requiring surgical, radiologic, or endoscopic intervention. |
| Enterocutaneous fistula requiring intervention | 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. |
| • Other outcomes | |
| Incisional hernia | Incisional hernia is defined as full-thickness discontinuity in abdominal wall and bulging of abdominal contents, with or without obstruction. |
| Pancreaticocutaneous fistula | Output through a percutaneous drain or drainage canal after removal of drains from a surgical wound, or any measurable volume of fluid with an amylase content >3 times the serum amylase level. |

**Supplementary table S2**. Definitions of the primary and secondary outcomes (*continued*)

| | |
|---|---|
| Wound infection | A superficial incisional SSI (surgical site infection) and must meet the following criterion: infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and the patient has at least 1 of the following:<br>- Purulent drainage from the superficial/deep incision but not from the organ/space component of the surgical site<br>- Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision<br>- At least 1 of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion<br>- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiologic examination<br>- Diagnosis of superficial/deep incisional SSI by the surgeon or attending physician |
| Exocrine pancreatic insufficiency | Oral pancreatic-enzyme supplementation required to treat clinical symptoms of steatorrhea; this requirement was not present before onset of pancreatitis. |
| Endocrine pancreatic insufficiency | The need for insulin or oral-diabetic drugs; this requirement was not present before onset of pancreatitis. |
| Recurrent acute pancreatitis | Recurrence of acute pancreatitis is defined as a new episode of acute pancreatitis, as defined by the 2012 Revised Atlanta criteria, after complete resolution of all symptoms associated with the previous acute pancreatitis episode. |
| Chronic pancreatitis | Defined according to the M-ANNHEIM criteria. |

**Supplementary table S3.** Baseline characteristics of the POINTER trial

| **Characteristics** | **Immediate Drainage (*n* = 55)** | **Postponed Drainage (*n* = 49)** |
|---|---|---|
| Age (yr) | 60 (14) | 59 (11) |
| Male sex | 32 (58) | 32 (65) |
| Cause of pancreatitis | | |
| Gallstones | 36 (65) | 29 (59) |
| Alcohol abuse | 8 (15) | 7 (14) |
| Disease severity | | |
| Admitted to intensive care unit | 15 (27) | 13 (27) |
| SIRS | 47 (85) | 40 (82) |
| Organ failure | 13 (24) | 8 (16) |
| Multiple organ failure | 8 (15) | 6 (12) |
| CT severity index[a] | 7 ± 2 | 6 ± 2 |
| Extent of pancreatic necrosis | | |
| <30% | 35 (64) | 33 (68) |
| 30-50% | 8 (15) | 7 (14) |
| >50% | 12 (22) | 9 (18) |
| Encapsulation of necrosis | | |
| Not encapsulated | 6 (11) | 8 (16) |
| Medium encapsulated | 16 (29) | 19 (39) |
| Largely encapsulated | 19 (35) | 11 (22) |
| Fully encapsulated | 14 (25) | 11 (22) |
| Diagnosis of infected necrosis | | |
| Gas configuration | 20 (36) | 16 (33) |
| Positive fine needle aspiration | 6 (11) | 11 (22) |
| Suspected clinically | 29 (53) | 22 (45) |
| Onset of symptoms to diagnosis of necrotising pancreatitis/ necrotic collection (days) | 8 ± 8 | 9 ± 7 |
| Onset of symptoms to diagnosis of infected necrosis (days) | 21 ± 6 | 19 ± 7 |

*Data are presented as no. (%) or mean (SD). CT = computed tomography, SIRS = Systemic Inflammatory Response Syndrome. [a]Data were derived from the contrast-enhanced CT performed before randomization. Scores may range from 0 to 10, with higher scores indicating more extensive pancreatic and peripancreatic necrosis.*

**Supplementary table S4.** All-cause mortality after the initial 6-month follow-up per individual patient

| **Immediate-drainage** | **Cause of death** | **Age** | **Pancreatitis related** | **Time (months)[a]** |
|---|---|---|---|---|
| 1 | Obstructive shock of unknown cause | 72 | No | 8 |
| 2 | Multiple causes not related to pancreatitis | 69 | No | 9 |
| 3 | Fistula of the gastrointestinal-tract (patient requested life-sustaining treatment withdrawal) | 70 | Yes | 10 |
| 4 | Infected pancreatic necrosis in combination with COVID-19 infection (patient requested life-sustaining treatment withdrawal) | 57 | Yes | 48 |
| **Postponed-drainage** | **Cause of death** | **Age** | **Pancreatitis related** | **Time (months)[a]** |
| 1 | Cholangiocarcinoma | 57 | No | 26 |
| 2 | Gastric cancer | 75 | No | 44 |
| 3 | Respiratory failure of unknown cause | 56 | No | 57 |
| 4 | Lung cancer | 74 | No | 62 |

[a] *Time between randomization and date of death.*

**Supplementary table S5**. Drainage procedures after the initial 6-month follow-up per individual patient

| **Immediate-drainage** | **Type of drainage** | **Indication** | **Time (months)** [a] |
|---|---|---|---|
| 1 | - PCD (5x) | Persistent pancreatic fluid collection | 7 |
| 2 | - PCD | Recurrent pancreatic fluid collection (recurrent acute pancreatitis) | 49 |
| 3 | - PCD | Persistent pancreatic fluid collection (disconnected pancreatic duct) | 20 |
| 4 | - ETD | Recurrent pancreatic fluid collection | 7 |
| 5 | - ETD | Recurrent pancreatic fluid collection (disconnected pancreatic duct) | 9 |
| 6 | - PCD | Recurrent pancreatic fluid collection (disconnected pancreatic duct) | 23 |
| 7 | - ETD | Persistent pancreatic fluid collection | 15 |
| **Postponed-drainage** | **Type of drainage** | **Indication** | **Time (months)** [a] |
| 1 | - PCD | Persistent pancreatic fluid collection | 11 |
| 2 | - ETD | Recurrent pancreatic fluid collection (recurrent acute pancreatitis) | 22 |
| 3 | - ETD<br>- PCD (20x) | Recurrent infected necrotic collections (recurrent acute pancreatitis) | 19 |

*Patients per group who required (additional) drainage procedures after the initial 6-months follow-up. ETD = endoscopic transluminal drainage. PCD = percutaneous catheter drainage. [a] Time between randomisation and date of first drainage procedure after the initial 6-months follow-up.*

**Supplementary table S6.** Sensitivity analyses: Primary outcome and interventions in patients whom diagnosis was based on clinical suspicion for infected necrosis[a]

| | **New events after the initial 6-month follow-up** (excluding events as initially reported in the POINTER trial) | | | | **Total follow-up**[b] (time between randomization and the end of long-term follow-up) | | | |
|---|---|---|---|---|---|---|---|---|
| **Outcome** | **Immediate Drainage (*n* = 24/47)** | **Postponed Drainage (*n* = 18/41)** | **Relative risk (95% CI)** | **P-value** | **Immediate Drainage (*n* = 29/54)** | **Postponed Drainage (*n* = 20/46)** | **Relative risk (95% CI)** | **P-value** |
| Primary outcome | | | | | | | | |
| Major complications or death – no. (%) | 3 (13) | 3 (17) | 0.75 (0.17-3.29) | 1.00 | 15 (52) | 9 (45) | 1.15 (0.63-2.09) | 0.64 |
| Interventions | | | | | | | | |
| Catheter Drainage – no. (%) | 4 (17) | 3 (17) | 1.00 (0.26-3.92) | 1.00 | 29 (100) | 14 (70) | 1.43 (1.07-1.90) | 0.00 |
| Necrosectomy – no. (%) | 0 | 0 | - | - | 18 (62) | 4 (20) | 3.10 (1.24-7.80) | 0.00 |
| Median total surgical, endoscopic, and radiologic interventions for infected necrosis (IQR) – no. | 0 (0-0) | 0 (0-0) | - | 0.94 | 4 (2-7) | 2 (0-5) | - | 0.06 |
| Median total drainage procedures (IQR) - no. | 0 (0-0) | 0 (0-0) | - | 0.94 | 2 (1-5) | 1 (0-4) | - | 0.07 |
| No. of drainage procedures (%) – no. of patients (%) | | | | | | | | |
| 0 | 20 (83) | 15 (83) | - | - | 0 | 6 (30) | - | - |
| 1 | 4 (17) | 2 (11) | - | - | 13 (45) | 7 (35) | - | - |
| 2 | 0 | 0 | - | - | 2 (7) | 0 | - | - |
| ≥3 | 0 | 1 (1) | - | - | 14 (48) | 7 (35) | - | - |
| Median total necrosectomies (IQR) – no. | 0 (0-0) | 0 (0-0) | - | - | 1 (0-3) | 0 (0-0) | - | 0.03 |
| No. of necrosectomies – no. of patients (%) | | | | | | | | |
| 0 | 24 (100) | 18 (100) | - | - | 11 (38) | 16 (80) | - | - |
| 1 | 0 | 0 | - | - | 6 (21) | 0 | - | - |
| 2 | 0 | 0 | - | - | 3 (10) | 0 | - | - |
| ≥3 | 0 | 0 | - | - | 9 (31) | 4 (20) | - | - |

*Data are presented as no. (%) or median (IQR). [a]Multiple events in the same patient were scored as one outcome. [b]4 patients (of the originally 104 included patients) from the POINTER trial did not consent to participate in this follow-up study and were therefore missing in the total follow-up analysis. ICU = intensive care unit.*

**Supplementary table S7.** Exocrine and endocrine pancreatic function over time[a]

| Outcome | Total (n=79) | Immediate Drainage (*n* = 42) | Postponed Drainage (*n* = 37) |
|---|---|---|---|
| Exocrine pancreatic insufficiency[b] | | | |
| No | 42 (53) | 23 (55) | 19 (51) |
| Recovered | 6 (8) | 1 (2) | 5 (14) |
| Persistent | 25 (32) | 15 (36) | 10 (27) |
| New-onset | 6 (8) | 3 (7) | 3 (8) |
| Endocrine pancreatic insufficiency[c] | | | |
| No | 44 (56) | 23 (55) | 21 (57) |
| Recovered | 4 (5) | 1 (2) | 3 (8) |
| Persistent | 14 (18) | 7 (18) | 7 (19) |
| New-onset | 17 (22) | 11 (26) | 6 (16) |

*Data are presented as no. (%). [a]Pancreatic function at the end of long-term follow-up compared to the pancreatic function at 6-month follow-up. Data from questionnaires were obtained from all but one surviving patients (n=79).[b] Defined as pancreatic enzyme use. [c]Defined as diabetes medication use.*