ORIGINAL ARTICLE

Immediate versus Postponed Intervention for Infected Necrotizing Pancreatitis

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ABSTRACT

BACKGROUND

Infected necrotizing pancreatitis is a potentially lethal disease that is treated with the use of a step-up approach, with catheter drainage often delayed until the infected necrosis is encapsulated. Whether outcomes could be improved by earlier catheter drainage is unknown.

METHODS

We conducted a multicenter, randomized superiority trial involving patients with infected necrotizing pancreatitis, in which we compared immediate drainage within 24 hours after randomization once infected necrosis was diagnosed with drainage that was postponed until the stage of walled-off necrosis was reached. The primary end point was the score on the Comprehensive Complication Index, which incorporates all complications over the course of 6 months of follow-up.

RESULTS

A total of 104 patients were randomly assigned to immediate drainage (55 patients) or postponed drainage (49 patients). The mean score on the Comprehensive Complication Index (scores range from 0 to 100, with higher scores indicating more severe complications) was 57 in the immediate-drainage group and 58 in the postponed-drainage group (mean difference, –1; 95% confidence interval [CI], –12 to 10; P=0.90). Mortality was 13% in the immediate-drainage group and 10% in the postponed-drainage group (relative risk, 1.25; 95% CI, 0.42 to 3.68). The mean number of interventions (catheter drainage and necrosectomy) was 4.4 in the immediate-drainage group and 2.6 in the postponed-drainage group (mean difference, 1.8; 95% CI, 0.6 to 3.0). In the postponed-drainage group, 19 patients (39%) were treated conservatively with antibiotics and did not require drainage; 17 of these patients survived. The incidence of adverse events was similar in the two groups.

CONCLUSIONS

This trial did not show the superiority of immediate drainage over postponed drainage with regard to complications in patients with infected necrotizing pancreatitis. Patients randomly assigned to the postponed-drainage strategy received fewer invasive interventions. (Funded by Fonds NutsOhra and Amsterdam UMC; POINTER ISRCTN Registry number, ISRCTN33682933.)

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*A complete list of the Dutch Pancreatitis Study Group members is provided in the Supplementary Appendix, available at NEJM.org.

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Acute pancreatitis is the most common pancreatic disease worldwide.[1] Necrotizing pancreatitis develops in approximately 20 to 30% of patients with acute pancreatitis.[2,3] Pancreatic and peripancreatic necrosis that becomes infected nearly always leads to invasive intervention.[3]

The current standard approach for infected necrotizing pancreatitis is a minimally invasive step-up approach with catheter drainage as the first step.[4,5] International guidelines advise postponement of catheter drainage and administration of antibiotics until the infected pancreatic and peripancreatic necrosis has become encapsulated; such walled-off necrosis usually takes 4 weeks to develop.[4-6] One rationale for postponement of an invasive intervention is to prevent complications, but this rationale originated from the era when open surgical necrosectomy was performed, and postponement may be less important for minimally invasive interventions.[3,7-9] Another important benefit of postponing drainage is that treatment with antibiotics may make invasive intervention unnecessary.[3,10,11]

Postponed catheter drainage is, however, subject to debate. In an international survey of expert pancreatologists, 45% reported that they recommend immediate catheter drainage as soon as infected pancreatic and peripancreatic necrosis is diagnosed.[12] In addition, a recent clinical practice guideline from the American Gastroenterological Association states that catheter drainage should be strongly considered when there is a concern of infection, even in the early phase of disease.[13]

In the current era of minimally invasive percutaneous and endoscopic transluminal interventions, walled-off necrosis theoretically might not be required for safe catheter drainage.[14-16] However, whether earlier catheter drainage leads to improved patient outcomes is not known. We therefore performed a multicenter, randomized superiority trial to investigate whether immediate catheter drainage is superior to postponed catheter drainage in patients with infected necrotizing pancreatitis.

METHODS

TRIAL DESIGN AND OVERSIGHT

The POINTER (Postponed or Immediate Drainage of Infected Necrotizing Pancreatitis) trial was an investigator-initiated, multicenter, randomized, controlled superiority trial conducted at 22 centers in collaboration with the Dutch Pancreatitis Study Group. The trial protocol (available with the full text of this article at NEJM.org) has been published previously.[17]

A Quick Take is available at NEJM.org

The Amsterdam UMC (Academic Medical Center location) ethics committee and the ethics committees at all participating centers approved the trial protocol. Written informed consent was obtained from each patient or the patient's legal representative. The trial was conducted in accordance with the principles of the Declaration of Helsinki. Clinical trial monitoring was performed by an independent monitor. A data and safety monitoring committee assessed patient recruitment and repeated patient safety evaluations after the enrollment of every 25 consecutive patients.

The trial was funded by Fonds NutsOhra and Amsterdam UMC. The funders had no role in the design or conduct of the trial or in the interpretation of the results. Access to the data was not restricted by confidentiality agreements. The principal investigators designed the trial protocol with the steering committee. Data were collected by the coordinating investigators and analyzed by the first author. The first author wrote the first draft of the manuscript. All the coauthors interpreted the data, collaborated on the manuscript preparation, and vouch for the fidelity of the trial to the protocol. The corresponding author had full access to all data and vouches for the completeness and accuracy of the data.

TRIAL POPULATION

Patients with acute pancreatitis were followed from the time of hospital admission by the trial coordinators at the 22 participating centers. Patients in whom necrotizing pancreatitis developed were assessed for the presence of infected peripancreatic and pancreatic necrosis (i.e., infected necrosis). When infected necrosis was suspected or confirmed, the nationwide online multidisciplinary expert panel of the Dutch Pancreatitis Study Group was consulted to evaluate the eligibility of the patient for randomization and the indication for intervention.[18] Patients with infected necrotizing pancreatitis who could undergo image-guided percutaneous or endoscopic transluminal drainage within 35 days after onset of symptoms of acute pancreatitis were

eligible to undergo randomization. Key exclusion criteria were symptoms of acute pancreatitis for more than 35 days and previous intervention for necrotizing pancreatitis. Additional exclusion criteria and details regarding trial design are provided in the Supplementary Appendix, available at NEJM.org.

DEFINITION OF INFECTED NECROSIS

In the first 14 days after onset of acute pancreatitis, we defined infected necrosis by a positive Gram's stain or culture from a fine-needle aspiration or the presence of gas configurations within pancreatic and peripancreatic necrosis on contrast-enhanced computed tomography (CT). In this time period, to avoid misclassification of early systematic inflammatory response syndrome as sepsis, we did not consider the presence of clinical signs of infected necrosis as the sole criterion to be diagnostic. After the first 14 days after onset, clinical signs of infection were considered diagnostic for infected necrosis, defined as persistent organ failure in patients admitted to the intensive care unit or the persistence of two inflammatory variables (temperature >38.5°C or elevated C-reactive protein levels or leukocyte counts) during 3 consecutive days in patients on regular hospital wards.

TRIAL PROCEDURES

Patients were randomly assigned, in a 1:1 ratio, to immediate catheter drainage or postponed catheter drainage. Randomization was performed by the trial coordinators, who used a centrally operated computer system and variable block randomization for concealment of treatment assignments. Randomization was stratified according to the presence or absence of failure of at least one organ system at randomization, disease duration (≤20 days or 21 to 35 days), and hospital volume (on the basis of expected inclusion rates).

Immediate catheter drainage included treatment with antibiotics and catheter drainage within 24 hours after randomization (which occurred as soon as infected necrosis was diagnosed on the basis of the aforementioned criteria). Postponed catheter drainage included treatment with antibiotics and supportive treatment aimed at postponing the drainage procedure until the stage of walled-off necrosis, when necrotic collections were largely or fully encapsulated. Full encapsulation was not mandatory in the case of patients whose condition was deteriorating. Patients assigned to the postponed-drainage group who presented with collections that were already largely or fully encapsulated were treated initially with antibiotics, with catheter drainage performed later in patients with clinical deterioration or lack of improvement. Image-guided percutaneous catheter drainage and endoscopic transluminal drainage were both allowed as a first step. In patients with insufficient clinical improvement within 72 hours, thin drains were replaced with larger drains. If catheter drainage was clinically unsuccessful, minimally invasive necrosectomy was performed (either videoscopic-assisted retroperitoneal débridement or endoscopic transluminal necrosectomy, depending on the route of initial drainage).

Follow-up was completed 6 months after randomization. Outpatient follow-up visits, which included abdominal imaging and evaluation of exocrine and endocrine pancreatic function, were scheduled at 3 months and 6 months.

END POINTS

The primary end point was the score on the Comprehensive Complication Index, including all complications that occurred between randomization and 6-month follow-up, graded according to the Clavien–Dindo classification.[19-21] The Comprehensive Complication Index is a validated tool, calculated as the sum of all complications weighted according to severity, that provides a continuous overall score from 0 (no complications) to 100 (death) for each patient.[19-21] Secondary end points were death; some of the major complications included in the Comprehensive Complication Index (new-onset organ failure [pulmonary, cardiovascular, renal, and multiple], bleeding resulting in intervention, perforation of a visceral organ leading to intervention, enterocutaneous fistula, pancreaticocutaneous fistula, incisional hernia, wound infection, and endocrine and exocrine pancreatic insufficiency); number of patients with severe complications (Clavien–Dindo classification of III or higher on a scale from I to V, with higher grades indicating more life-threatening complications); number of patients according to Clavien–Dindo classification; total number of surgical, endoscopic, and radiologic interventions (catheter drainage and necrosectomy); total length of in-

tensive care and hospital stay; and total inpatient hospital costs. All potential end points were evaluated by an adjudication committee whose members were unaware of the group assignments. Two experienced abdominal radiologists reassessed abdominal images.

STATISTICAL ANALYSIS

A difference of 10 points on the Comprehensive Complication Index reflects a one-grade difference in the Clavien–Dindo classification, an association based on a previous validation study that assessed the Comprehensive Complication Index as an end point in randomized trials.[20] Because infected necrotizing pancreatitis is a heterogeneous disease associated with substantial morbidity, we calculated the sample size by hypothesizing a clinically relevant 15-point reduction in the Comprehensive Complication Index from a mean (±SD) of 40±27 (on the basis of the number of complications observed in previous randomized trials conducted by the Dutch Pancreatitis Study Group) to 25.[22,23] Assuming a two-sided alpha level of 5%, a power of 80%, and a 2% loss to follow-up, we calculated the total sample size to be 104 patients.

All analyses were based on the intention-to-treat principle. There were no patients with missing data for the primary end point and few with missing data for the secondary end points; all observed data were included in the analysis without imputation for missing data. Results are presented as relative risks with corresponding confidence intervals or as mean differences with two-sided bias-corrected and accelerated 95% confidence intervals derived by bootstrapping with 5000 samples.[24,25] A two-sided P value of less than 0.05 indicates statistical significance for the primary end point. There was no plan for adjustment for multiple comparisons in the analyses of secondary end points, and the widths of confidence intervals were not adjusted for multiplicity; therefore, these results should not be used to infer definitive treatment effects. We performed exploratory analyses to examine the treatment in prespecified subgroups for the primary end point. Other post hoc exploratory analyses are described in the Supplementary Appendix. Total inpatient hospital costs were calculated from a hospital perspective (i.e., all hospital-related costs for inpatient care, including hospital and intensive care unit admission, laboratory tests, microbiologic tests, diagnostic imaging, endoscopy, radiologic interventions, and surgical procedures). Outpatient hospital costs and other health care costs (e.g., visits to a general practitioner or physiotherapist, formal home care, and nursing home care) were not included. A health economic analysis that was prespecified in the trial protocol has not been completed. Statistical analyses were conducted with R software, version 3.6.1 (R Project for Statistical Computing).

RESULTS

ENROLLMENT AND RANDOMIZATION

From August 2015 through October 2019, a total of 932 patients with necrotizing pancreatitis were assessed for eligibility (Fig. 1), and 104 patients were randomly assigned to immediate catheter drainage (55 patients) or postponed catheter drainage (49 patients). In the immediate-drainage group, 51 patients (93%) underwent catheter drainage within 24 hours after randomization. The remaining four patients (7%) underwent drainage after a mean of 4 days after randomization: one patient because of a spontaneous rupture of the necrotic collection and three patients for logistic reasons. One patient (2%) in the postponed-drainage group underwent catheter drainage within 24 hours after randomization owing to clinical deterioration.

Baseline characteristics were similar in the two groups (Table 1). Immediate catheter drainage was performed after a mean of 24 days (median, 24 days; interquartile range, 20 to 30) after onset of symptoms and postponed catheter drainage after a mean of 34 days (median, 29 days; interquartile range, 24 to 40) after onset of symptoms (mean difference, –10 days; 95% confidence interval [CI], –19 to –5) (Fig. S1). At the time of drainage, pancreatic and peripancreatic necrosis was largely or fully encapsulated in 33 patients (60%) in the immediate-drainage group and in 21 patients (70%) in the postponed-drainage group (Fig. S2).

PRIMARY AND SECONDARY END POINTS

We found no difference between the groups in the primary end point: the mean Comprehensive Complication Index score was 57 in the immediate-drainage group and 58 in the postponed-drainage group (mean difference, –1; 95% CI,

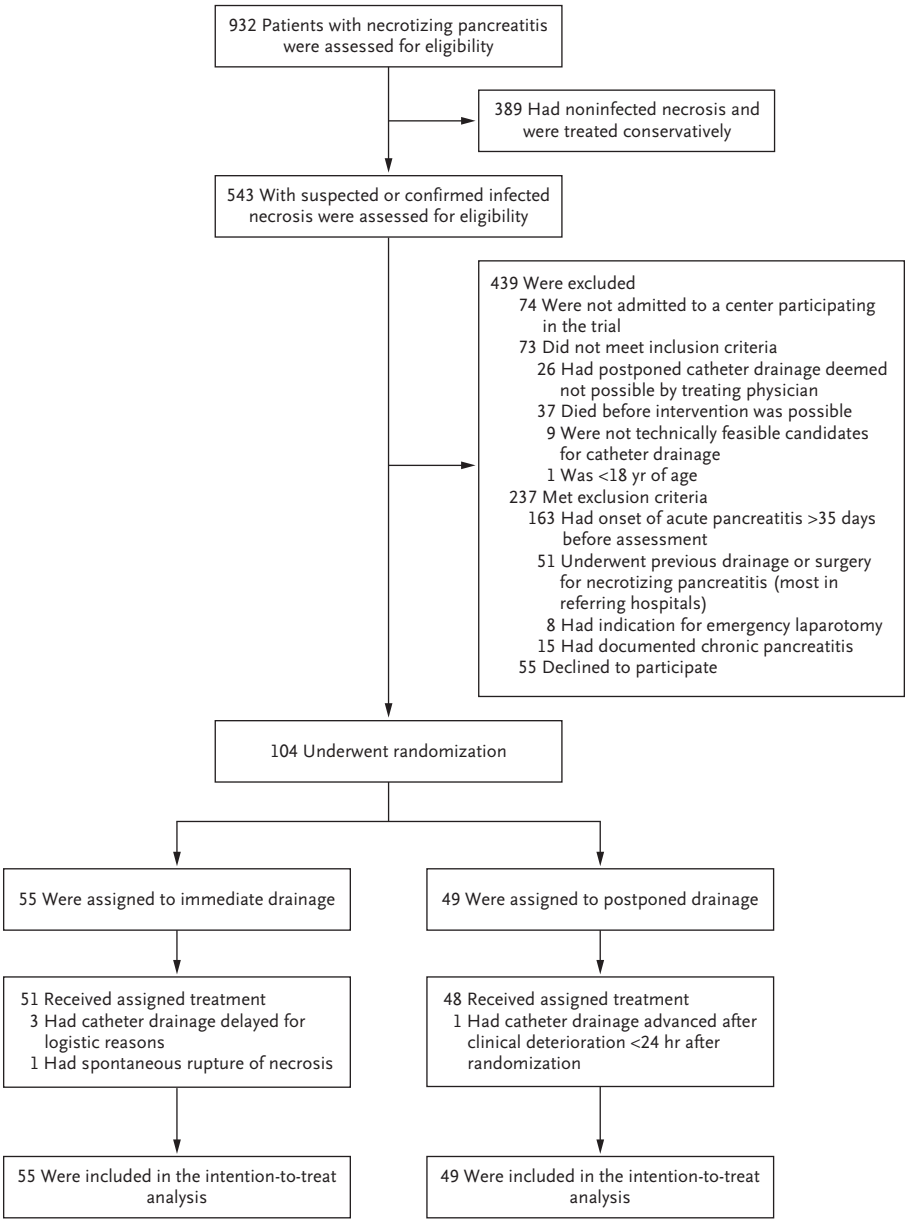

Figure 1. Screening, Randomization, and Follow-up.

At eligibility screening, 74 patients were excluded because clinical or logistic reasons prevented their transfer to a participating trial center. Of the 26 patients who did not meet inclusion criteria because postponed catheter drainage was deemed not possible, 18 were excluded owing to clinical deterioration despite organ-support therapy in the intensive care unit. Three patients assigned to receive immediate drainage had catheter drainage delayed owing to insufficient staff capacity and anesthesia considerations.

–12 to 10; P=0.90) (Table 2). Mortality was 13% in the immediate-drainage group, as compared with 10% in the postponed-drainage group (relative risk, 1.25; 95% CI, 0.42 to 3.68). No significant differences were found in the incidence of major complications, including new-onset organ failure (25% in the immediate-drainage group and 22% in the postponed-drainage group; relative risk, 1.13; 95% CI, 0.57 to 2.26); bleeding (15% and 20%, respectively; relative risk, 0.71;

95% CI, 0.31 to 1.66); perforation of a visceral organ, enterocutaneous fistula, or both (9% and 8%, respectively; relative risk, 1.11; 95% CI, 0.32 to 3.91); pancreaticocutaneous fistula (11% and 8%, respectively; relative risk, 1.34; 95% CI, 0.40 to 4.46); incisional hernia (none in either group); and wound infection (none in the immediate-drainage group and 1% in the postponed-drainage group). Complications graded according to Clavien–Dindo classification are shown in Table 2 and Table S8. The incidence of adverse events was similar in the two groups (Table S7).

The mean length of hospital stay was 59 days in the immediate-drainage group and 51 days in the postponed-drainage group (mean difference, 8 days; 95% CI, −9 to 23). Length of stay in the intensive care unit did not differ between the groups (mean difference, 0; 95% CI, −11 to 11) (Table 3).

The mean number of surgical, endoscopic, and radiologic interventions (catheter drainage and necrosectomy) was higher in the immediate-drainage group than in the postponed-drainage group (4.4 vs. 2.6; mean difference, 1.8; 95% CI, 0.6 to 3.0) (Table 3). In the postponed-drainage group, 19 patients (39%) were treated conservatively with antibiotics alone (without the need for drainage or necrosectomy); 17 of these patients survived. Ultimately, 28 patients (51%) in the immediate-drainage group required necrosectomy as compared with 11 patients (22%) in the postponed-drainage group. Infected necrosis was confirmed by gas on contrast-enhanced CT or by a positive culture obtained from the first drainage procedure in 51 patients (93%) in the immediate-drainage group and 26 of the 30 patients (87%) in the postponed-drainage group who were not treated conservatively.

At the 6-month follow-up, there were no between-group differences in development of endocrine and exocrine pancreatic insufficiency (Table 2) or in total inpatient hospital costs (mean difference, €6,166; 95% CI, −12,968 to 23,361 [U.S. $7,845; 95% CI, −16,499 to 29,721]) (Table 3). Results of the prespecified subgroup analyses are provided in Table S3. Endoscopic transluminal drainage was the first drainage procedure performed in 31 patients (56%) in the immediate-drainage group and in 20 of the 30 patients (67%) in the postponed-drainage group who were not treated conservatively (Table S5).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Immediate Catheter Drainage (N=55)	Postponed Catheter Drainage (N=49)
Age — yr	60±14	59±11
Male sex — no. (%)	32 (58)	32 (65)
Cause of pancreatitis — no. (%)		
Gallstones	36 (65)	29 (59)
Alcohol abuse	8 (15)	7 (14)
Disease severity — no. (%)		
Admitted to intensive care unit	15 (27)	13 (27)
Systemic inflammatory response syndrome	47 (85)	40 (82)
Organ failure	13 (24)	8 (16)
Multiple organ failure	8 (15)	6 (12)
CT Severity Index score†	7±2	6±2
Extent of pancreatic necrosis — no. (%)		
<30%	35 (64)	33 (67)
30 to 50%	8 (15)	7 (14)
>50%	12 (22)	9 (18)
Encapsulation of necrosis — no. (%)		
Not encapsulated	6 (11)	8 (16)
Medium encapsulated	16 (29)	19 (39)
Largely encapsulated	19 (35)	11 (22)
Fully encapsulated	14 (25)	11 (22)
Means of establishing diagnosis of infected necrosis — no. (%)		
Gas configurations	20 (36)	16 (33)
Positive fine-needle aspiration	6 (11)	11 (22)
Clinical suspicion for infected necrosis	29 (53)	22 (45)
No. of days from onset of symptoms to diagnosis of necrotizing pancreatitis	8±8	9±7
No. of days from onset of symptoms to diagnosis of infected necrosis	21±6	19±7

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Additional baseline characteristics are provided in Table S1.
† Data were derived from contrast-enhanced computed tomography (CT) performed before patients underwent randomization. Scores on the CT Severity Index range from 0 to 10, with higher scores indicating more extensive pancreatic and peripancreatic necrosis.

DISCUSSION

This multicenter, randomized trial did not show the superiority of immediate catheter drainage over postponed catheter drainage in reducing

Table 2. Primary and Secondary End Points for the Intention-to-Treat Analysis.

End Point	Immediate Catheter Drainage (N=55)	Postponed Catheter Drainage (N=49)	Relative Risk or Mean Difference (95% CI)
Primary end point			
Comprehensive Complication Index score — mean (95% CI)*	57 (50 to 65)	58 (50 to 67)	–1 (–12 to 10)†
Secondary end points — no. (%)‡			
Death within 6 months	7 (13)	5 (10)	1.25 (0.42 to 3.68)
New-onset organ failure§	14 (25)	11 (22)	1.13 (0.57 to 2.26)
Pulmonary	5 (9)	8 (16)	0.56 (0.20 to 1.59)
Cardiovascular	11 (20)	9 (18)	1.09 (0.49 to 2.40)
Renal	3 (5)	4 (8)	0.67 (0.16 to 2.84)
New-onset multiple organ failure	4 (7)	8 (16)	0.45 (0.14 to 1.39)
Bleeding	8 (15)	10 (20)	0.71 (0.31 to 1.66)
Perforation of a visceral organ or enterocutaneous fistula	5 (9)	4 (8)	1.11 (0.32 to 3.91)
Pancreaticocutaneous fistula	6 (11)	4 (8)	1.34 (0.40 to 4.46)
Incisional hernia	0	0	—
Wound infection	0	1 (2)	—
Exocrine insufficiency			
Use of enzymes	20 (36)	19 (39)	0.94 (0.57 to 1.54)
Fecal elastase <200 mg/g¶	25 (48)	14 (32)	1.51 (0.90 to 2.53)
Endocrine insufficiency	11 (20)	10 (20)	0.98 (0.46 to 2.11)
Clavien–Dindo ≥III complication‖	42 (76)	40 (82)	0.94 (0.77 to 1.14)

* The Comprehensive Complication Index is calculated as the sum of all complications weighted according to severity. Continuous overall scores range from 0 (no complications) to 100 (death). P=0.90 for the mean difference between the groups.
† Shown is the mean difference between groups.
‡ Confidence intervals for secondary end points were not adjusted for multiple comparisons; therefore, no definite conclusions can be drawn from these data.
§ New-onset organ failure was defined as organ failure that was not present at the time the patient underwent randomization.
¶ Data were missing for three patients in the immediate-drainage group and five patients in the postponed-drainage group.
‖ Clavien–Dindo complications in this category include those that resulted in surgical, endoscopic, or radiologic intervention (Clavien–Dindo grade III), required care in the intensive care unit (Clavien–Dindo grade IV), or resulted in death (Clavien–Dindo grade V).

complications in patients with infected necrotizing pancreatitis. Patients randomly assigned to the immediate-drainage group underwent more interventions for infected necrosis, whereas the postponed-drainage strategy averted the need for intervention in more than one third of the patients assigned to that group.

Our results do not support the hypothesis that catheter drainage performed immediately after diagnosis of infected necrosis leads to better patient outcomes with fewer complications than postponed drainage. These findings differ from those of previous retrospective studies.[14,15] A recent retrospective study involving 193 patients with necrotizing pancreatitis assessed outcomes after early treatment (76 patients treated <4 weeks after disease onset) as compared with standard treatment (117 patients treated ≥4 weeks after disease onset) with an endoscopically centered step-up approach and showed similar incidences of complications in the two groups. However, patients in the early-treatment group had longer hospital stays than patients in the standard-treatment group, and a

Table 3. Secondary End Points Related to Health Care Utilization.*

End Point	Immediate Catheter Drainage (N=55)	Postponed Catheter Drainage (N=49)	Relative Risk (95% CI)	Mean Difference (95% CI)
Catheter drainage — no. (%)	55 (100)	30 (61)	1.63 (1.31 to 2.04)	
Necrosectomy — no. (%)	28 (51)	11 (22)	2.27 (1.27 to 4.06)	
Mean total surgical, endoscopic, and radiologic interventions for infected necrosis (95% CI) — no.	4.4 (3.6 to 5.3)	2.6 (1.8 to 3.6)		1.8 (0.6 to 3.0)
Mean total catheter drainage procedures (95% CI) — no.	3.1 (2.6 to 3.8)	1.9 (1.3 to 2.8)		1.2 (0.3 to 2.2)
No. of catheter drainage procedures — no. of patients (%)				
0	0	19 (39)		
1	20 (36)	15 (31)		
2	8 (15)	2 (4)		
≥3	27 (49)	13 (27)		
Mean total necrosectomies (95% CI) — no.	1.3 (0.8 to 1.9)	0.7 (0.3 to 1.3)		0.6 (–0.1 to 1.2)
No. of necrosectomies — no. of patients (%)				
0	27 (49)	38 (78)		
1	13 (24)	4 (8)		
2	3 (5)	1 (2)		
≥3	12 (22)	6 (12)		
Mean length of stay in ICU (95% CI) — days	12 (6 to 23)	12 (6 to 23)		0 (–11 to 11)
Mean length of stay in hospital (95% CI) — days	59 (50 to 70)	51 (40 to 65)		8 (–9 to 23)
Mean total inpatient hospital costs (95% CI)†				
€	52,914 (43,783 to 67,860)	46,747 (35,194 to 64,642)		6,166 (–12,968 to 23,361)
$	67,321 (55,704 to 86,336)	59,475 (44,776 to 82,242)		7,845 (–16,499 to 29,721)

* Confidence intervals for secondary outcomes were not adjusted for multiple comparisons; therefore, no definite conclusions can be drawn from these data. Percentages may not total 100 because of rounding. ICU denotes intensive care unit.

† Costs are expressed for the year 2019. Costs were converted to U.S. dollars with the use of the Organization for Economic Cooperation and Development (OECD) purchasing power parities for 2019 (€0.786 equivalent to U.S. $1).

higher percentage of patients in the early-treatment group died (13% vs. 4%, P=0.02).[14] Similarly, another recent retrospective study compared outcomes of 38 patients treated with endoscopic transluminal drainage (19 patients treated <4 weeks after disease onset vs. 19 patients treated ≥4 weeks after disease onset) and showed that patients in the group treated less than 4 weeks after disease onset had a longer hospital stay than patients in the group treated 4 weeks or more after disease onset (median, 26 days vs. 6 days; P<0.01) but with no difference in the incidence of death.[15] Both studies, however, had retrospective, nonrandomized designs, which clearly limits the interpretation of the results.

In this trial, the Comprehensive Complication Index scores and mortality did not differ significantly between the groups. Nevertheless, some unexpected benefits were noted with regard to the postponed-drainage approach. First, patients in the postponed-drainage group required fewer interventions for infected necrosis. In particular, the percentage of patients who required necrosectomy in the postponed-drainage group was lower than the 49 to 57% and 32 to 97% reported in two recent randomized trials.[22,26] Second, 35% of patients in the postponed-drainage group were successfully treated conservatively with antibiotics only. Antibiotic treatment was successful more often than was anticipated

on the basis of the 3 to 16% success reported in the literature.[3,10,11] Although the mean between-group difference in the time from onset of symptoms to catheter drainage was only 10 days, this postponement period was sufficient to identify patients whose condition could improve with antibiotic treatment alone. Whether improvement of antimicrobial therapy leads to better outcomes for patients with this condition, including a higher rate of conservative treatment, is an important issue for future research.

On the other hand, immediate catheter drainage did not lead to worse outcomes in terms of complications and mortality. In general, this trial therefore also showed that in case of rapid clinical deterioration, early catheter drainage is a valid treatment option.

This trial has some limitations. First, for the primary end point, we used scores on the Comprehensive Complication Index, which was originally developed to assess postoperative complications.[19-21] However, because no other scoring systems combine all types and severity of complications, the Comprehensive Complication Index was deemed the most suitable for this trial. Although the high Comprehensive Complication Index scores in both groups illustrate the high morbidity associated with infected necrotizing pancreatitis, the clinically important difference in patients with such high scores is currently unclear. We cannot exclude the possibility that a larger trial would have identified significant differences in Comprehensive Complication Index scores between the groups. Second, the trial protocol allowed for both endoscopic and surgical step-up approaches. The endoscopic route has gradually become the preferred treatment strategy.[22,26] Nevertheless, not all collections with pancreatic and peripancreatic necrosis can be reached endoscopically. The trial design therefore reflects current clinical practice. Third, a considerable number of patients were not eligible to undergo randomization. The main reason was that, more often than anticipated, infected necrosis was diagnosed after the 35-day cutoff. This cutoff point was chosen to reflect the clinical scenario of hospitalized patients in whom infected necrotizing pancreatitis developed rather than patients who were previously hospitalized and then readmitted for infected necrosis and typically treated without further delay.[27] In addition, there were patients not eligible for randomization because catheter drainage had already been performed or because postponing catheter drainage was not considered feasible. However, given the large number of patients screened for eligibility, the number who were ineligible (26 patients) seems to represent only a minority of patients with infected necrotizing pancreatitis.

This trial did not show the hypothesized benefit of earlier catheter drainage in patients with infected necrotizing pancreatitis. With a postponed drainage strategy that included antibiotic treatment, fewer interventions for infected necrosis were performed and more than one third of patients were treated conservatively. These findings suggest that an initial conservative approach with antibiotics is justified when infected necrosis is diagnosed. Future studies may focus on this treatment approach, including ways to improve the appropriate use of antibiotic treatment.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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