ORIGINAL ARTICLE

Timing of Surgical Intervention in Necrotizing Pancreatitis

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Objective: To determine the effect of timing of surgical intervention for necrotizing pancreatitis.

Design: Retrospective study of 53 patients and a systematic review.

Setting: A tertiary referral center.

Main Outcome Measure: Mortality.

Results: Median timing of the intervention was 28 days. Eighty-three percent of patients had infected necrosis and 55% had preoperative organ failure. The mortality rate was 36%. Sixteen patients were operated on within 14 days of initial admission, 11 patients from day 15 to 29, and 26 patients on day 30 or later. This latter group received preoperative antibiotics for a longer period ($P < .001$), and *Candida* species and antibiotic-resistant organisms were more often cultured from the pancreatic or peripancreatic necrosis in these patients ($P = .02$). The 30-day group also had the lowest mortality (8% vs 75% in the 1 to 14–days group and 45% in the 15 to 29–days group, $P < .001$); this difference persisted when outcome was stratified for preoperative organ failure. During the second half of the study, necrosectomy was further postponed (43 vs 20 days, $P = .06$) and mortality decreased (22% vs 47%, $P = .09$). We also reviewed 11 studies with a total of 1136 patients. Median surgical patient volume was 8.3 patients per year (range, 5.3-15.6), median timing of surgical intervention was 26 days (range, 3-31), and median mortality was 25% (range, 6%-56%). We observed a significant correlation between timing of intervention and mortality ($R = -0.603$; 95% confidence interval, −2.10 to −0.02; $P = .05$).

Conclusion: Postponing necrosectomy until 30 days after initial hospital admission is associated with decreased mortality, prolonged use of antibiotics, and increased incidence of *Candida* species and antibiotic-resistant organisms.

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Timing of surgical intervention in acute necrotizing pancreatitis (ANP) has changed substantially during the last decade, from early necrosectomy, without respect to the state of infection, to delayed operation in case of documented or suspected infection of pancreatic necrosis. It has been hypothesized that postponing surgical intervention allows the immune system to encapsulate the necrotic tissue, thus technically facilitating necrosectomy and potentially reducing mortality.[1] The beneficial effect of this strategy was confirmed in a randomized controlled trial comparing intervention within 72 hours of onset with operation after 12 days.[2] There was a reduction in mortality from 56% to 27% in patients who underwent operation after 12 days. Consequently, recent surgical guidelines of the International Association of Pancreatology (IAP) state that surgical intervention should preferably be performed between 15 and 28 days (in the third or fourth week) after admission.[3] A recent European survey demonstrated that there is still no consensus on this subject, as 43% of surgeons prefer intervention within the first 14 days, whereas 29% prefer to wait for at least 21 days.[4] Furthermore, it was recently suggested that the delay in surgical intervention in ANP may lead to prolonged use of (prophylactic) antibiotics, leading to an increased incidence of *Candida* infections and antibiotic-resistant organisms.[5]

This study describes our increasing experience in postponing surgical intervention in necrotizing pancreatitis. This strategy may lead to necrosectomy being performed after the upper end of the interval suggested by the IAP guidelines, ie, after day 28. Furthermore, we assessed the impact of postponing surgical intervention on the use of antibiotics, fungal infections, and antibiotic resistance. Finally, we performed a systematic literature review to further explore potential associations between timing of surgical intervention and outcome.

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METHODS

TREATMENT PROTOCOL

We performed a search in the patient database of our tertiary referral center for the *International Classification of Diseases, Ninth Revision* (*ICD-9*), code for acute pancreatitis (577.0) in patients admitted from January 1995 to December 2004. Acute pancreatitis was diagnosed in 445 patients with clinical signs of acute abdominal pain and a serum amylase level above 1000 U/L (16.67 μkat/L). Pancreatic necrosis was detected using contrast-enhanced computed tomography. Fine needle aspiration (FNA) was only used if the outcome would influence the clinical strategy, ie, in a patient in whom the clinical signs of infected necrosis were not convincing. Antibiotic prophylaxis was used in most patients in whom pancreatic or peripancreatic necrosis was detected. Antibiotics were used in all patients with documented or clinical suspicion of infection of pancreatic or peripancreatic necrosis. Indication for necrosectomy was either persisting organ failure despite maximum medical management and/or documented infected necrosis. The surgical treatment results were previously described.[6] In the first year of the current series, our preferred strategy changed from an open abdomen approach[7] to closed lavage as described by Beger et al.[8] Patients were managed either on the nursing ward, the medium-care unit, or on the intensive care unit (ICU).

SURGICAL STRATEGY

During laparotomy, the abdomen was inspected and blunt debridement of necrotic tissue was performed. Two double-lumen drainage tubes were inserted through separate incisions with their tips in the lesser sac and necrotic cavities. The abdomen was closed afterwards and local continuous lavage was started. Intervention was performed again because packing gauzes had been left in situ, but it was mainly reperformed because of clinical deterioration.

VARIABLES

In the 53 consecutive adult patients who underwent necrosectomy, the following variables were collected: age, sex, Acute Physiology and Chronic Health Evaluation II (APACHE II) score during the first 24 hours, Ranson score during the first 48 hours, comorbidity, etiology of pancreatitis, time of first surgical intervention, organ failure at the time of first surgical intervention, results of microbiologic cultures for bacteria and *Candida*, exposure to broad-spectrum antibiotics (amoxicillin/clavulanate, piperacillin/tazobactam, and imipenem/cilastatin), exposure to all antibiotics, duration of stay in the ICU, duration of hospital stay, and mortality during the hospital stay. If patients were referred from other hospitals, data from the initial admission were used to calculate preoperative hospital stay (timing of operation), APACHE II and Ranson scores, ICU and hospital stay, and antibiotic use. Antibiotic prophylaxis was defined as all antibiotics administered prior to the detection of infected necrotizing pancreatitis. Groups were analyzed on the basis of the timing from initial admission to the first surgical intervention: within 14 days, from day 15 to 29, or 30 days or later. These cutoff points were chosen in accordance with IAP guidelines.[3]

ORGAN FAILURE

Organ failure was defined as PaO_2 less than 60 mm Hg despite receiving 4 L of oxygen per minute via a nasal tube or need for mechanical ventilation (pulmonary insufficiency); a serum creatinine level greater than 2.0 mg/dL (152.2 μmol/L) or need for hemofiltration or hemodialysis (renal failure); systolic blood pressure less than 90 mm Hg or need for catecholamine support (cardiocirculatory insufficiency); and a serum calcium level less than 7.48 mg/dL (1.87 mmol/L) or a thrombocyte level less than 100×10^3/μL (100×10^9/L; metabolic disorder). This definition was adapted from the Atlanta symposium.[9] Multiple organ failure was defined as failure of 2 or more organ systems.

MICROBIOLOGY

Intra-abdominal cultures were available from all 53 patients who were operated on. Culture results were derived from the hospital's central microbiology database and were checked by a single microbiologist (B.U.R.). The following genera and species were considered resistant to antibiotics, as they are intrinsically resistant to or have a high risk of becoming resistant to therapy with third-generation cephalosporins: *Acinetobacter, Enterobacter cloacae, Enterobacter aerogenes, Pseudomonas, Stenothrophomonas maltophililia*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococci*. All *Candida* species cultured from intra-abdominal specimens (ie, FNA material, lavage fluid, and tissue obtained at operation) were documented. A primarily positive *Candida* culture was defined as a positive *Candida* culture during FNA before the first necrosectomy or from material obtained during the first surgical intervention. All cultures for bacteria and *Candida* were performed using standard microbiologic methods.

TREATMENT TRENDS

To detect differences in treatment strategy over time, the 10-year period was divided into 2 periods of 5 years (1995-1999 and 2000-2004). The following variables were compared: prevalence of acute pancreatitis, timing of intervention since first hospital admission, antibiotic prophylaxis, patient referral, culturing of *Candida* species and antibiotic-resistant organisms, hospital and ICU stay, and mortality.

SYSTEMATIC REVIEW

Our MEDLINE search comprised the following terms: *acute pancreatitis*, *surgery*, and *necrosectomy*. A cross-reference search was performed in the studies found. The search was limited to studies published in the previous 10 years (January 1, 1996, to January 1, 2006). Only papers published in the English language were included. To diminish the influence of selection bias, only studies that had at least 25 consecutive patients who underwent surgical intervention for ANP were included. Furthermore, the studies had to contain data on time of surgical intervention for the entire study population and mortality; subgroups of patients were not allowed. Data of a single arm of a randomized controlled trial were allowed, since the randomization process essentially excludes selection bias. Finally, because patient series are frequently described in multiple publications, only the last publication of a single institution was included.[6] Outcome parameters were patient volume (number of patients operated on for ANP per year), documented infection of pancreatic or peripancreatic necrosis, timing of surgical intervention, and mortality.

STATISTICAL ANALYSIS

Categorical data were compared using the Fisher exact test. Results of continuous data are presented as median (range). Comparison of continuous variables with a skewed distribution was

Table 1. Baseline Characteristics on Admission for Necrotizing Pancreatitis[a]

Characteristic	Time From Initial Admission to Operation			P Value
	Day 1-14 (n=16)	Day 15-29 (n=11)	Day ≥30 (n=26)	
Timing of operation from admission, d	7 (1-13)	22 (15-28)	48 (30-164)	
Male sex, No. (%)	8 (50)	7 (64)	19 (73)	.32
Age, y	57 (30-72)	57 (38-74)	58 (29-73)	.89
Patients referred, No. (%)	11 (69)	10 (91)	21 (81)	.37
Ranson score	5 (2-8)	4 (2-7)	3 (2-7)	.13
APACHE II score	9 (3-21)	11 (4-19)	9 (2-14)	.57
Comorbidity, No. (%)				
Cardiovascular	6 (38)	1 (9)	5 (19)	.19
Renal	5 (31)	2 (18)	5 (19)	.61
Pulmonary	5 (31)	2 (18)	2 (8)	.14
Diabetes	0	0	2 (8)	.34
Etiology, No. (%)				
Biliary	4 (25)	3 (27)	15 (57)	.06
Alcohol	2 (13)	2 (18)	3 (12)	.86
Endoscopic retrograde cholangiopancreatography	1 (6)	2 (18)	3 (12)	.63
Other/unknown	9 (56)	4 (37)	5 (19)	.048

Abbreviation: APACHE II, Acute Physiology and Chronic Health Evaluation II.
[a]Values are median (range) unless otherwise indicated.

performed using Mann-Whitney or Kruskal-Wallis tests. Logistic regression was used to determine which factors contributed to mortality. Odds ratios are given with their respective 95% confidence intervals. Correlations between continuous outcomes were explored by linear regression. A 2-tailed $P \leq .05$ was considered statistically significant.

RESULTS

During the 10-year period, 445 patients with acute pancreatitis were admitted (55% men; median age, 53 years [range, 18-86]). Fifty-three ANP patients underwent necrosectomy (34 men; median age, 57 years [range, 29-75]). Forty-two patients (79%) had been referred from other hospitals, all for surgical intervention. In total, 403 patients were admitted primarily; 11 of these patients underwent surgical intervention. Therefore, 2.7% (11 of 403) of the patients primarily admitted to our hospital had surgical interventions for acute pancreatitis.

FIRST SURGICAL INTERVENTION

Median timing of the operation was 28 days (mean, 35 days [range, 1-105 days]). Sixteen patients (30%) were operated on from day 1 to 14; 11 patients (21%) from day 15 to 29; and 26 patients (49%) from day 30 and on. The median APACHE II score on admission was 9 (range, 2-21). Baseline characteristics, etiology, and comorbidity did not differ between the 3 groups (**Table 1**).

INDICATION FOR INTERVENTION

At the time of first surgical intervention, 29 patients (55%) had organ failure, 12 patients in 1 organ, 7 patients in 2 organs, and 10 patients in 3 or more organs. Thirty patients (57%) had been admitted or were admitted to the ICU. Neither preoperative organ failure ($P = .2$) nor ICU admission ($P = .41$) differed among the 3 groups. **Table 2** presents patient characteristics at the first surgical intervention. Thirty of 53 (57%) patients had preoperative FNA; microorganisms were cultured in 22 patients (73%). The 8 patients with negative FNA results were all operated on because of their deteriorating clinical condition. In 4 of these 8 patients, microorganisms were cultured from the intraoperative samples, representing a negative predictive value of 50% for FNA. Of the 23 patients without a preoperative FNA, 18 patients (78%) had microorganisms cultured. Overall, infected ANP was documented in 44 of 53 patients (83%). Infected ANP was most often documented in the group of patients who were operated on at day 30 or later ($P = .2$) (Table 2). Four patients were operated on without organ failure or infected necrosis; 3 of these patients were initially operated on in referring hospitals for unclear reasons, and 1 patient, primarily admitted, was operated on for persisting high fevers.

ANTIBIOTICS

Forty-five (85%) patients received antibiotic prophylaxis. The median duration of antibiotic treatment prior to first intervention was 14 days (range, 0-77), with a median of 2 antibiotics used (range, 0-9). Patients operated on at day 30 or later more often received antibiotic prophylaxis for longer than 30 days ($P = .04$) and received antibiotics for a longer period ($P < .001$), whereas the number of antibiotics used prior to the first necrosectomy did not differ ($P = .14$) (Table 2). During the entire admission, the median total length of antibiotic treatment was 38 days (range, 1-200), and the length of broad-spectrum antibiotic treatment was 22 days (range, 0-82); a median of 4 antibiotics were used (range, 1-12). During admission, patients in the 30 or more–days group received antibiotics ($P = .001$) and broad-

Table 2. Characteristics at Time of First Surgical Intervention for Necrotizing Pancreatitis

Characteristic	Time From Initial Admission to Operation: Day 1-14 (n=16)	Day 15-29 (n=11)	Day ≥ 30 (n=26)	P Value
Infected necrosis, No. (%)	10 (63)	9 (82)	25 (96)	.02
Preoperative organ failure, No. (%)	11 (69)	7 (64)	11 (42)	.2
Preoperative multiple organ failure, No. (%)	6 (38)	5 (45)	6 (23)	.35
Absence of both infected necrosis and organ failure, No. (%)	3 (19)	0 (0)	1 (4)	.12
Intensive care unit admission, No. (%)	9 (56)	8 (73)	13 (50)	.41
Intensive care unit stay, No. of patients				
1-7 d	5	3	6	.18
8-14 d	4	0	2	
≥15 d	0	5	5	
Antibiotic prophylaxis > 30 d, No. (%)	0	1 (9)	10 (38)	.04
Median time of antibiotic use (range), d	4 (0-11)	17 (0-29)	25 (0-77)	< .001
Median No. of antibiotics used (range)	1 (0-3)	2 (0-6)	2 (0-9)	.14
Primary *Candida* or resistant microorganism, No. (%)	1 (6)	1 (6)	9 (35)	.05
Primary *Candida* infection, No. (%)	0	0	4 (15)	.11
Primary resistant microorganism, No. (%)	1 (6)	1 (6)	6 (23)	.28

Table 3. Clinical Course and Outcome of Necrotizing Pancreatitis[a]

Characteristic	Time From Initial Admission to Operation: Day 1-14 (n=16)	Day 15-29 (n=11)	Day ≥ 30 (n=26)	P Value
Antibiotic use, d	15 (2-200)	46 (16-78)	42 (1-102)	.001
Broad-spectrum antibiotic use, d	12 (0-38)	28 (0-66)	26 (0-82)	.002
Antibiotics used	1 (1-6)	6 (2-12)	5 (1-10)	.08
Candida infection during admission, No. (%)	6 (38)	7 (64)	12 (46)	.46
Antibiotic-resistant microorganism during admission, No. (%)	6 (38)	5 (45)	19 (73)	.06
No. of interventions	4 (1-15)	3 (1-14)	3 (1-19)	.44
Re-intervention, No. (%)	12 (75)	9 (82)	19 (73)	.28
Total intensive care unit stay, d	16 (0-61)	31 (0-82)	19 (0-88)	.49
Hospital stay, d	29 (4-146)	85 (41-131)	108 (6-237)	< .001

[a] Values are median (range) unless otherwise indicated.

spectrum antibiotics ($P = .002$) for a longer period. The number of antibiotics used did not differ between the groups ($P = .08$) (**Table 3**).

CANDIDA SPECIES

Candida species were isolated in 25 patients (47%). In 19 patients, only 1 *Candida* species was found, usually *C albicans* (n=15). Combinations of *C albicans*, *C glabrata*, *C parapsilosis*, and *C tropicalis* were found in 6 patients. In 1 patient, *Candida* was cultured from a blood sample 1 month after hospital admission. By that time, the patient had received 11 different antibiotics; he died 1 month later of multiple organ failure. The incidence of positive fungal cultures during admission did not differ between the groups ($P = .46$) (Table 3).

ANTIBIOTIC-RESISTANT MICROORGANISMS

In 30 patients (57%), antibiotic-resistant microorganisms were cultured. In 24 patients (45%), 1 resistant microorganism was cultured, and in 6 patients, multiple resistant species were cultured. Methicillin-resistant *Staphylococcus aureus* was cultured in only 1 patient. *Candida* species or resistant organisms were more often cultured during FNA or during the first surgical intervention in the 30 or more–days group ($P = .05$) (Table 2). During admission, more resistant microorganisms were cultured in this group ($P = .06$) (Table 3).

ORGAN FAILURE AND OUTCOME

Overall mortality was 36% (19 of 53 patients). Mortality in patients without organ failure at the time of first operation was 21% (5 of 24), 33% (4 of 12) in patients with preoperative single organ failure, and 59% (10 of 17) in patients with multiple organ failure ($P = .02$). Of the 4 patients operated on with failure of 4 organ systems, all within 14 days, mortality was 100%. **Table 4** compares the 3 groups with stratification for organ failure. In all strata (no organ failure, organ failure, and multiple organ failure), outcome was better in the group of patients who underwent operation at day 30 or later ($P = .045$, $P < .001$, and $P = .001$, respectively). There was

Table 4. Hospital Mortality for Necrotizing Pancreatitis Stratified for the Presence of Organ Failure at Time of First Intervention

	Time From Initial Admission to Operation, No. (%)			
Hospital Mortality	Day 1-14 (n=16)	Day 15-29 (n=11)	Day ≥30 (n=26)	*P* Value
Patients without organ failure	3/5 (60)	0/4 (0)	2/15 (13)	.045
Patients with organ failure	9/11 (82)	5/7 (71)	0/11 (0)	< .001
Patients with multiple organ failure	6/6 (100)	4/5 (80)	0/6 (0)	.001
Total	12/16 (75)	5/11 (45)	2/26 (8)	< .001

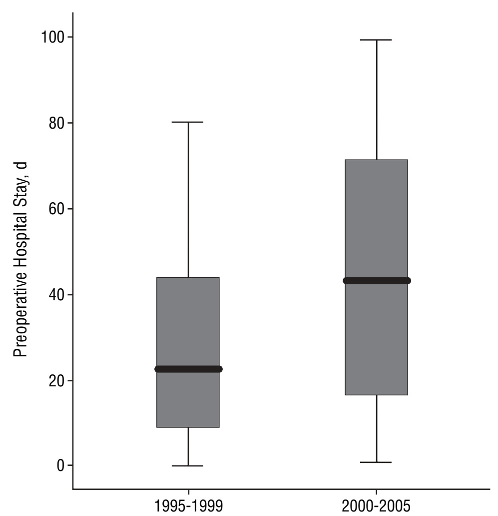

Figure 1. Time from initial admission to surgical intervention in necrotizing pancreatitis during a 10-year period. Horizontal lines show the median.

a trend toward decreased mortality in patients operated on from 15 to 29 days compared with patients operated on within the first 14 days (5 of 11 [45%] vs 12 of 16 [75%], respectively; *P*=.08). In the 30 or more–days group, mortality was further improved compared with patients operated on from 15 to 29 days (2 of 26 [8%] vs 5 of 11 [45%], respectively; *P*=.02). Total median hospital stay was 89 days, 109 days for survivors and 35 days for nonsurvivors.

RISK FACTORS

Patients with preoperative organ failure had higher mortality (48% vs 21%, *P*=.04). There was no significant difference in mortality between (1) infected and noninfected pancreatic necrosis groups (32% vs 56%, respectively; *P*=.26), (2) patients with positive vs negative *Candida* cultures (36% in both groups), (3) patients with and patients without antibiotic-resistant organisms (27% vs 48%, respectively; *P*=.15), and (4) referred and primarily admitted patients (38% vs 27%, respectively; *P*=.73). There was no mortality in the 4 patients with sterile FNA before microorganisms were cultured from the intraoperative samples. Table 3 gives an overview of the clinical course in relation to timing of the operation. Model building by means of logistic regression demonstrated that, with age and sex entered as confounders, operation within 30 days (odds ratio, 28.2; 95% confidence interval, 4.72-168.0; *P*<.001) and the presence of preoperative multiple organ failure (odds ratio, 0.151; 95% confidence interval, 0.023-0.967; *P*=.03) were the only factors with an effect on mortality.

Table 5. Changes in the Treatment of Acute Pancreatitis During a 10-Year Period[a]

Characteristic	1995-1999	2000-2004	*P* Value
Acute pancreatitis			
No. of patients admitted with acute pancreatitis[b]	210	235	
Male sex, No. (%)	105 (50)	145 (62)	.02
Age, y	53 (21-80)	53 (18-86)	.36
Hospital stay, d	16 (1-181)	14 (1-266)	.003
Mortality, No. (%)	28 (13)	21 (9)	.92
Surgical intervention			
No. of patients who underwent necrosectomy	30	23	
Male sex, No. (%)	18 (60)	16 (70)	.57
Age, y	57 (29-75)	58 (38-67)	.87
Referral, No. (%)	26 (87)	16 (70)	.18
Antibiotic prophylaxis, No. (%)	24 (80)	20 (87)	.72
Preoperative organ failure, No. (%)	17 (57)	12 (52)	.79
Preoperative multiple organ failure, No. (%)	10 (33)	7 (30)	> .99
Infected necrosis, No. (%)	24 (80)	20 (87)	.72
Timing of operation, d	20 (1-80)	43 (1-164)	.06
1-14, No. (%)	11 (37)	5 (22)	
15-29, No. (%)	8 (27)	3 (13)	
≥ 30, No. (%)	11 (37)	15 (65)	
Postoperative stay survivors	84 (11-138)	45 (9-159)	.08
Mortality, No. (%)	14 (47)	5 (22)	.09

[a] All values are median (range) unless otherwise indicated.
[b] All acute pancreatitis patients admitted, including those treated surgically.

TREATMENT TRENDS

Figure 1 demonstrates that in the second 5-year period, pancreatic necrosectomy was performed at a later stage of disease (*P*=.06). This was accompanied by a trend toward lower mortality (*P*=.09) (**Table 5**). For all acute pancreatitis patients (including those conservatively treated), a slight but significant reduction in median hospital stay was observed during the second 5-year period (*P*=.003).

SYSTEMATIC REVIEW

Of 123 manuscripts reviewed, only 10 studies contained the required data on timing and outcome (**Table 6**).[2,10-18] Several studies, though fulfilling all other inclusion criteria, did not mention timing of surgical intervention for the entire population and consequently were excluded.[12,15,19-26] The results of the delayed operation arm

Table 6. Systematic Review of Series With at Least 25 Patients Operated on for Necrotizing Pancreatitis

Source	Design	No. of Patients	No. of Patients Operated On/y	Patients With Infection, %	Median Time From Initial Admission to Operation, d	Mortality, %
Mier,[2] 1997	Randomized controlled	25	8.3	60	2	56
Fernandez-del Castillo,[10] 1998	Retrospective	64	9.1	56	31	6
Branum,[11] 1998	Retrospective	50	8.3	84	27	12
Farkas,[12] 1998	Retrospective	203	11.3	100	20	15
Büchler,[13] 2000	Prospective	28	5.6	96	22	21
Ashley,[14] 2001	Retrospective	36	7.2	92	27	11
Beattie,[15] 2002	Retrospective	54	6.8	68	26	43
Götzinger,[16] 2003	Prospective	250	15.6	74	15	39
Connor,[17] 2005	Prospective	88	14.7	77	31	28
Rau,[18] 2005	Retrospective/prospective	285	15	49	13	25
Present study	Retrospective	53	5.3	83	28	36
Total, median		54	8.3	77	26	25

from the Mier et al[2] trial were excluded, as this group only consisted of 11 patients. A review of 1136 patients from 11 series (including the present series) was performed. The median number of patients operated on for necrotizing pancreatitis was 8.3 per center per year; median timing of first surgical intervention was 26 days; and mortality was 25%. An association was observed between (postponed) timing and (decreased) mortality ($R=-0.603$; 95% confidence interval, −2.10 to −0.02; $P=.05$) (**Figure 2**). No association between patient volume (number of acute pancreatitis patients operated on per year) and mortality ($P=.93$) nor between infection of pancreatic necrosis and mortality ($P=.32$) could be demonstrated.

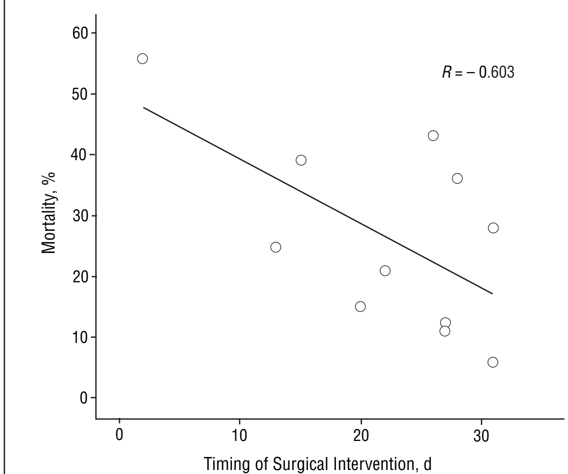

Figure 2. Association between time of surgical intervention (from initial admission) for necrotizing pancreatitis and mortality.

COMMENT

Current surgical guidelines recommend performing necrosectomy in infected necrotizing pancreatitis between days 15 and 28 after onset of disease.[3] In contrast, the present series demonstrates that surgical intervention performed after day 29 is associated with a lower mortality rate. This postponed intervention does lead to prolonged use of antibiotics with a concomitant increase in the incidence of fungal infections and infections with antibiotic-resistant microorganisms from pancreatic necrosis. Also, in the systematic review, a significant association between postponed timing of surgical intervention and lower mortality was observed. Interestingly, the median time of first surgical intervention in the review was 26 days, demonstrating that nearly 50% of ANP patients in tertiary referral centers are operated on after the interval indicated by the IAP guidelines.

In a randomized controlled trial, Mier et al[2] showed that delaying intervention in patients with ANP beyond the first 12 days is beneficial compared with operating within 72 hours. These results are reflected in the IAP guidelines, which state that an early operation, within 14 days after onset of the disease, is not recommended in patients with necrotizing pancreatitis.[3] Our results do indeed show a trend toward decreased mortality for intervention in the third and fourth weeks compared with the first 14 days. However, mortality was further improved significantly if surgical intervention was performed after day 29.

Although APACHE II scores on admission were similar, the mortality in this series (36%) is higher as reported in 3 large series from the United States (10% in 150 patients).[10,11,14] However, the present mortality, and especially the 22% mortality in the last 5 years, does not differ greatly from mortality reported in 6 European tertiary referral centers (29% in 908 patients).[12,13,15-18] Because intercontinental timing of intervention did not differ in the review, the explanation for this difference in mortality has not yet been found.

During our study period, the worldwide trend to postpone operations influenced our management of ANP patients. This strategy has been adopted more and more in our hospital since the turn of the century. This is reflected by the delayed intervention in the second study period. There is no data to suggest that patients treated in the second 5 years of the study period differed in severity of pancreatitis from the patients treated in the first 5 years. All patients were treated at our surgical medium-care unit and

ICU, at which the treatment for acute pancreatitis patients did not essentially change during the 10-year study period. Therefore, apparently it is possible to delay surgical intervention in a subgroup of ANP patients.

Strikingly, there was no mortality in patients with multiple organ failure operated on 30 or more days after initial admission. Because these patients had similar preoperative ICU stays as the other 2 groups, it is clear that they developed multiple organ failure at a later stage of their disease. The patients in the 30 or more–days group developed multiple organ failure at a later stage of their disease. The stratification further indicates that surgical intervention in patients with multiple organ failure within the first 14 days carries a mortality of 100% and may therefore be omitted. Because improved intensive care treatment makes it possible to essentially avoid mortality within the first 2 weeks,[27] it would also seem possible to withhold surgical intervention within the first 2 weeks.

In the literature, there is only 1 study that reports on the outcome of surgical intervention in ANP after the first 4 weeks of admission. Fernández-del Castillo et al[10] reported on 64 consecutive ANP patients requiring surgical intervention in a 7-year period. This study's data also suggests that intervention in the weeks preceding day 27 has the likelihood of a worse outcome compared with intervention in the weeks after day 27 (C. Fernández-del Castillo, MD, personal communication, February 24, 2006). Because of the impressive low overall mortality (6.2%) in their series, the difference in mortality between both groups did not reach significance.

The incidence of cultures positive for *Candida* and antibiotic-resistant organisms in this series is relatively high; fortunately, neither influenced mortality. In the literature, there is controversy regarding the relevance of fungal infection. Three retrospective studies demonstrated a higher mortality in cases of fungal infection,[28-30] whereas 2 prospective studies failed to demonstrate such an effect.[31,32] No study has yet demonstrated an effect of antibiotic resistance on mortality in acute pancreatitis. It may well be that restrictive use of broad-spectrum (prophylactic) antibiotics will decrease the number of infections with *Candida* and antibiotic-resistant microorganisms. Because 2 recent placebo-controlled trials[33,34] did not show any evidence for the use of antibiotic prophylaxis, we are currently tailoring our antibiotic treatment on the basis of blood, FNA, and intraoperative culture results. Some investigators also advocate for the use of percutaneous drainage of infected pancreatic or peripancreatic collections as a means of temporizing, or even averting, operating until day 30.[35]

The results of this systematic review are in line with the findings from our series. Although the demonstrated association between timing and mortality may not be considered proof of a causal relationship, the findings are very suggestive indeed. The fact that an association between patient volume and outcome could not be detected may be because only large series (>25 patients) from tertiary referral centers were included. As demonstrated by median timing of intervention in the review, apparently many tertiary referral centers worldwide postpone surgical intervention when possible.

Because this study is not a randomized controlled trial, selection bias may have played a role in the positive outcome in patients operated on after the first 29 days. However, both the APACHE II and Ranson scores were similar for the 3 groups. Furthermore, stratification for the presence of organ failure did not indicate the presence of any selection bias either. The systematic review may be subject to some extent of information bias, as several studies did not report data on timing of intervention.

In conclusion, our study demonstrates that necrosectomy for documented or suspected infected ANP performed after 29 days is associated with lower mortality. However, an increase in fungal colonization and resistant microorganisms is to be expected owing to the increased use of antibiotics. Our results also recommend tailored use of antibiotics and critical review of the patients' clinical condition to select cases in which the operation may be delayed. We feel that our study provides strong arguments to withhold surgical intervention in the first 14 days, even in the presence of multiple organ failure. Whenever possible, surgical intervention should be postponed until day 30. Based on the findings in this study, this strategy is currently being practiced in a Dutch randomized, controlled, multi-center trial on surgical intervention in infected necrotizing pancreatitis, which recently started including patients.[36,37] To compare interinstitutional data, future studies on surgical intervention in ANP should report on the median timing of first surgical intervention.

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