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Adverse Effects of Delayed Treatment for Perforated Peptic Ulcer

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Objective

The authors assessed the consequences of delayed treatment for ulcer perforation with regard to short-term and long-term survival, complication rates, and length of hospital stay.

Summary Background Data

Important adverse effects of delayed treatment have not been studied previously. Conflicting results have been given with regard to short-term survival.

Methods

One thousand two hundred ninety-two patients operated on for perforated peptic ulcer in the Bergen area between 1935 and 1990 were studied. The effect of delay on postoperative lethality and complications adjusted for age, sex, ulcer site, and year of perforation was analyzed by stepwise logistic regression. The effect of delay on duration of hospital stay adjusted for potential confounding factors was analyzed by Cox proportional hazards regression. Observed survival was estimated by the Kaplan-Meier method, and expected survival was calculated from population mortality data.

Results

Adverse effects increased markedly when delay exceeded 12 hours. Delay of more than 24 hours increased lethality sevenfold to eightfold, complication rate to threefold, and length of hospital stay to twofold, compared with delay of 6 hours or less. The reduced long-term survival for patients treated more than 12 hours after perforation could be attributed entirely to high postoperative mortality.

Conclusions

Delayed treatment after peptic ulcer perforation reduced survival, increased complication rates, and caused prolonged hospital stay. To improve outcome after ulcer perforation, an effort should be made to keep delay at less 12 hours, particularly in elderly patients.

Delayed treatment for perforated peptic ulcer may lead to negative consequences for the individual patients and for the surgical department. Clinicians know that treatment of an intestinal perforation is imperative and that survival of the patient depends on the time from perforation to operation. This relationship has been recognized since the turn of the century.[1,2] Delay in treatment can reduce health for the patients both on short and long term, and can adversely affect treatment costs by increas-

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ing length of hospital stay. Contrary to other prognostic variables (e.g., age, preoperative status, and coincidental disease), treatment delay can be modified. The problem of delay is particularly important because time from perforation to operation is increasing in Norway[3] and in other Western countries.[4-16]

We focused on potential adverse effects of treatment delay for 1292 patients treated for perforated peptic ulcer in Bergen between 1935 and 1990, taking into account the effect of potentially confounding factors such as age, sex, ulcer site, and year of perforation. The effect of delay on survival for up to 38 years after the perforation was studied in 1098 patients treated between 1952 and 1990 compared with controls matched by age, sex, and year of birth.

PATIENTS

One thousand two hundred ninety-two patients with perforated peptic ulcer (cancer perforations excluded) were admitted to two major hospitals in the Bergen area between 1935 and 1990. Twenty-one patients with missing data on treatment and 34 patients not operated on were excluded. Thus, 1237 patients who underwent surgical treatment were included in this analysis. The process of identifying the patients and establishing the database used for analyses has been described previously.[17]

Treatment delay denotes time from perforation to start of operation. Time of perforation (i.e., start of acute symptoms) was given in case notes or operating records and start of operation was given in anesthetic records. Such information was available for 1117 patients.

Short-Term Outcome

Relevant information was obtained from case notes and autopsy reports. Deaths due to perforation or complications during hospitalization were recorded (n = 85). Information on postoperative complications was based on temperature charts, radiology reports, bacteriology (culture), registrations of drug treatment, and doctor's follow-up comments. Three hundred fifty-one patients who experienced one or more complications or death were identified. Separate analyses were performed for the 166 patients with general complications (heart and respiratory problems) and the 137 patients with "infective complications" (wound infections, intra-abdominal abscesses). Hospital stay was defined as time from operation to discharge or death.

Long-Term Survival

Long-term survival was assessed by matching the patient file for the period 1952 to 1990 (n = 1136) against the Norwegian Death Registry (established in 1952). Twenty-four patients were immediately lost to follow-up because of identification problems, and 14 foreign citizens were excluded; thus, 1098 patients were studied. Of these patients, 503 were dead by December 31, 1990.

Site of perforation was recorded from the surgeons' description in the operation notes, supported by histology if available. For the purpose of this study, the ulcers were classified as duodenal (n = 1058), i.e., ulcers located in the duodenum, pyloric orifice, and prepyloric area (within 2 cm proximal to the pyloric orifice), or gastric (n = 157), i.e., located at other gastric sites.[7,17]

STATISTICAL METHODS

The associations between lethality and complication rates, and delay, age, year of perforation, ulcer site, and sex were analyzed by stepwise logistic regression models. Nonsignificant independent variables were excluded from saturated models in a backward stepping manner using the LR program in BMDP.[18] Delay was categorized in 6-hour intervals. Age was dichotomized according to the median value. Year of perforation was categorized into three periods—1935 to 1950 (the year when antibiotics came into general use in ulcer perforation treatment[17]), 1951 to 1970, and 1971 to 1990. Odds ratios with 95% confidence intervals are presented. Because of the high prevalence of complications and deaths, some of the odds ratios do not approximate relative risks. Thus, relative risks are given in the text.

Associations between delay, age, year of perforation, ulcer site and sex and the time from surgery to discharge were analyzed using Cox proportional hazards regression models. The hazard denotes the risk of being discharged from hospital. Patients who died in the hospital were censored (they still would have been in hospital if they had not died). The analyses were performed using the 2L program in BMDP.[19] Delay, age, and year of perforation were entered as continuous variables, and ulcer site and sex were entered as dichotomous variables. Graphically displayed survival functions were estimated by the Kaplan-Meier method using the program 1L in BMDP.[20]

Patient survival was estimated by the Kaplan-Meier method and presented with 95% confidence bands. Expected survival was calculated from published population mortality rates. The expected survival curve is the curve expected for random population controls matched to the patient group by age, sex, and year of birth.[21]

RESULTS

Both median delay and median age were high among patients who died (Table 1). However, these patients spent little time in the hospital, indicating that most deaths occurred early in the postoperative period. Pa-

Table 1. GENERAL CHARACTERISTICS FOR ALL PATIENTS, PATIENTS WHO DIED, PATIENTS WITH COMPLICATIONS, AND PATIENTS WHO SPENT >14 DAYS IN HOSPITAL

	All Patients (n = 1237)	Deaths (n = 85)	Complications (n = 351)	Hospital Stay >14 Days* (n = 320)
Delay (median, hrs)	7	14	9	8
Age (median, yrs)	49	66	55	49
Sex (% women)	19	29	21	16
Ulcer site (% gastric)	13	28	18	18
Hospital stay (median, days)	11	7	16	—

* 14 days was the upper quartile.

tients experiencing complications spent more time in hospital.

Table 2 gives lethality, complication rates, and duration of hospital stay related to delay stratified by age and year of perforation. Short-term outcome was associated significantly with delay in all subgroups except for hospital stay and complication rates in the period 1965 to 1990.

Lethality by treatment delay is given in Fig 1. The increase in lethality with increasing delay was consistent and seemed to accelerate when delay exceeded 12 hours. The effect of time period is illustrated in Fig 1A. Lethality decreased dramatically around 1950, but there has been no further improvement since then. The age effect and the effect of ulcer site is illustrated in Fig 1B. Lethality in patients of less than 50 years was very low. In the older patients, however, postoperative lethality increased sixfold with increasing delay. For gastric perforations, the increase in lethality with delay was less consistent. The risk was particularly high for patients with a delay of more than 24 hours.

Table 3 gives the influence of delay on postoperative lethality adjusted for age, year of perforation, and ulcer site as estimated by stepwise logistic regression. There was a gradual increase in odds ratios with increasing delay. The odds ratio was 9.35 (corresponding to a relative risk of 7–8) for the longest standing perforations compared with those with a duration of 6 hours or less. The

Table 2. POSTOPERATIVE LETHALITY, POSTOPERATIVE COMPLICATION RATES, AND HOSPITAL STAY ACCORDING TO DELAY STRATIFIED BY YEAR OF PERFORATION AND AGE (DELAY DIVIDED BY 75 PERCENTILE, AGE BY MEDIAN, YEAR BY MIDDLE OF PERIOD)

	Delay ≤12 hrs		Delay >12 hrs		p Value* (difference)
	No.	%	No.	%	
Lethality					
1935–64	19/385	4.9	13/74	17.6	<0.001
1965–90	15/508	3.0	28/150	18.7	<0.001
age <50 years	10/473	2.1	7/78	9.0	0.001
Age ≥50 years	24/410	5.9	33/145	22.8	<0.001
Complications					
1935–64	110/383	28.7	28/73	38.4	NS
1965–90	101/507	19.9	67/147	45.6	<0.001
age <50 years	111/483	23.0	25/77	32.5	0.07
age ≥50 years	100/407	24.6	69/142	48.6	<0.001
Hospital stay >14 days					
1935–64	147/392	37.5	31/77	40.3	NS
1965–90	51/484	10.5	48/143	33.6	<0.001
<50 years	121/496	24.4	31/77	40.3	0.003
≥50 years	77/380	20.3	48/142	33.8	0.001

* Chi square test.

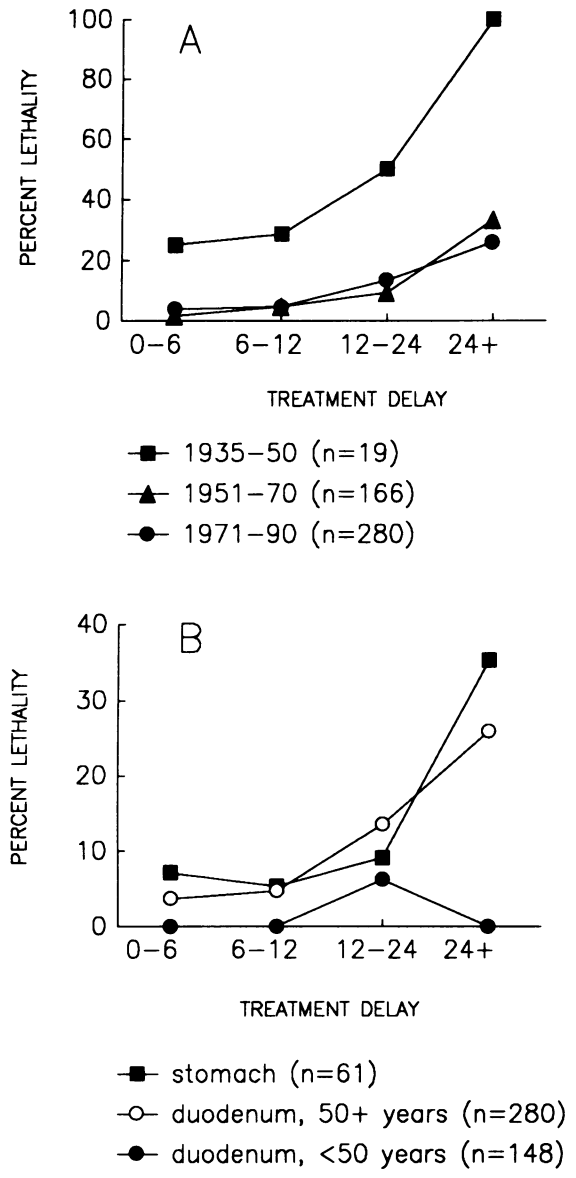

Figure 1. Lethality by treatment delay; (A) according to year of perforation (patients >50 years with duodenal perforations) and (B) according to ulcer site and age (patients treated 1971–1990).

fall in lethality around 1950 was highly significant, but when separate analyses were performed for the period 1951 to 1990, no significant time-dependent change in lethality after 1950 was found.

Complication rates by delay are given in Fig 2. Except for gastric perforations from 1971 to 1990, the relationship between delay and complication rates was consistent in all subgroups. The frequency of complications increased markedly when delay exceeded 12 hours. Complications decreased considerably after 1950, with no further improvements in the recent decades. Even during the last 20-year period, complication rates increased consistently with increasing delay in duodenal perforations, and the increase was larger for older patients.

Table 4 gives the effect of delay, age, ulcer site, and year of perforation on complication rates. The risk for complications increased gradually with increasing delay. The odds ratio was 5.99 (corresponding to a relative risk of approximately 3) for patients with delays of more than 24 hours compared with patients with delays of 6 hours or less. Complications increased with age and declined from the first to the second period of time with no further change after 1950. This result was confirmed in a separate analysis for the period 1951 to 1990, with a finer categorization of age (10-year age groups). Gastric perforations carried higher complication rates than duodenal perforations, but sex had no significant effect on complication rates.

The risk of having general complications increased for long delays, with an odds ratio of 7.6 for the longest standing perforations. The risk was greater for patients older than 50 years, and the risk decreased after 1950. No secular trend was seen after 1950 in a separate analysis performed for this period. Ulcer site was not of importance for the occurrence of general complications. Infective complications, however, were twice as common in gastric ulcer patients as in duodenal ulcer patients. Treatment delay had a significant effect on the risk of infective complications, but no age effect was found. The rate of postoperative infections decreased dramatically after 1950.

Fig 3 shows Kaplan-Meier estimates for duration of hospital stay by delay for patients treated between 1971 and 1990. Median hospital stay was 13 days for patients with long preoperative delays, compared with 7 days for patients with delays of 6 hours or less. There was a consistent increase in hospital stay for each group according

Table 3. EFFECT OF DELAY, AGE, YEAR OF PERFORATION, AND ULCER SITE ON POSTOPERATIVE LETHALITY ACCORDING TO STEPWISE LOGISTIC REGRESSION ANALYSIS

Variable	Level	OR	95% CI
Delay	≤6 hrs	1	
	7–12 hrs	1.24	0.59–2.58
	13–18 hrs	2.77	1.12–6.88
	19–24 hrs	3.03	0.99–9.24
	>24 hrs	9.35	4.41–19.8
Age	<50 years	1	
	≥50 years	6.24	3.01–12.9
Year	1935–50	1	
	1951–70	0.13	0.06–0.30
	1971–90	0.12	0.05–0.26
Ulcer site	Duodenum	1	
	Stomach	2.49	1.34–4.61

OR = odds ratio; CI = confidence interval.

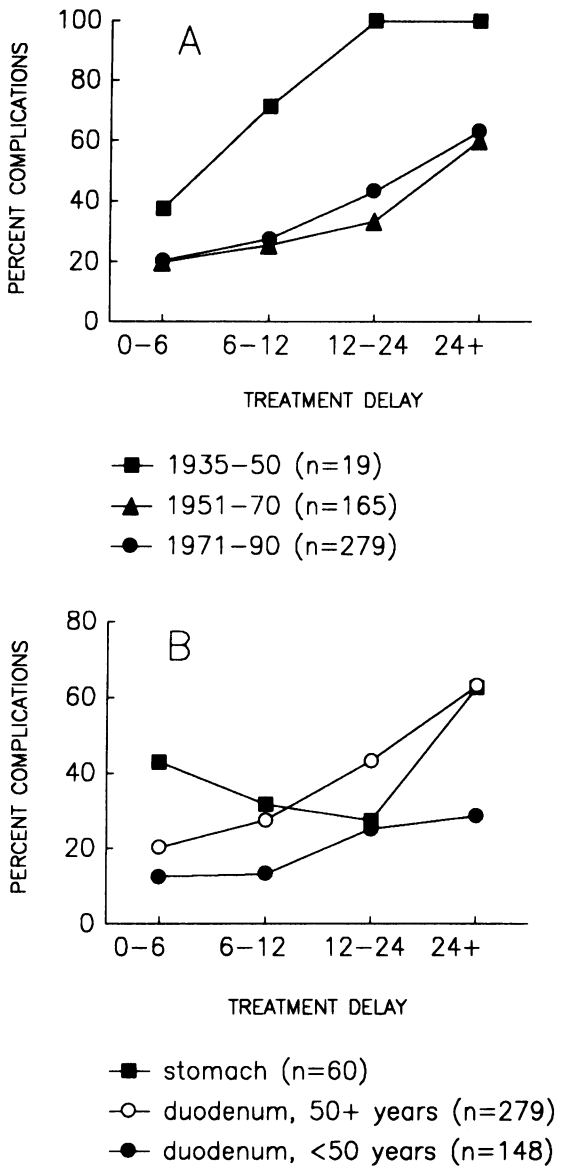

Figure 2. Postoperative complications by treatment delay; (A) according to year of perforation (patients >50 years with duodenal perforations), and (B) according to ulcer site and age (patients treated 1971–1990).

to delay; the increase was large when delays exceeded 12 hours.

Table 5 gives the effects of delay, age, ulcer site, and year of perforation on duration of hospital stay based on Cox proportional hazards regression analyses for the period 1955 to 1990. Long delay was associated significantly with a lower discharge rate from hospital and thus, longer hospital stay (reflected in the negative coefficient of −1.0128) (Table 5). Gastric perforations and old age were associated with longer hospital stay. There was a continuous shortening of hospital stay from 1955 to 1990. When only patients with uncomplicated ulcer perforation were included in the analysis, the effect of delay on hospitalization period was smaller and not significant, whereas the effect of age, year of perforation, and ulcer site still was significant.

Fig 4 gives observed and expected survival for up to 38 years after the perforation for patients treated within or beyond 12 hours after the perforation. Differences in age, sex, and year of perforation is taken care of in the calculation of expected survival. In patients treated within 12 hours after the perforation, the initial decrease in survival was barely significant, whereas survival the next 15 years was not significantly different from expected. Long-term survival was somewhat lower than expected from 15 to 30 years after the perforation. However, in patients treated more than 12 hours after perforation, survival the first year was reduced markedly. After the initial decrease, observed survival approximated expected survival for 15 years, indicating strong selection of healthy individuals due to poor treatment (long delay). When stratified by age, the survival patterns according to delay were similar for elderly and young patients (data not given). Thus, the effect of delay on survival can be attributed entirely to the initial difference in lethality.

DISCUSSION

Decades ago, concern about treatment delay was expressed frequently in the literature, and delay was shown to be related closely to postoperative lethality in large patient series.[8–11] Such concern rarely is found in contemporary literature, maybe because recent studies show diverging results on effect of delay.[2,4–7,22–24] A closer look at the published data, however, reveals that in all latter series, there are more deaths among patients with long-standing perforations. Nonsignificant findings may be because of low statistical power or adjustment for preoperative shock.[6,23,24] Such adjustment is not correct in evaluating the influence of delay on outcome because shock can be a link in the causal chain between delay and outcome.

In our study, we found a strong association between duration of delay and outcome, also for the most recent years. The association was consistent for both lethality, complication rates, and prolonged hospital stay, it was highly statistically significant in all analyses, and it was evident in graphical displays of stratified data.

However, the influence of delay on outcome could be biased by several mechanisms. First, patients experiencing long delays often are in poor condition and unable to give reliable information on symptom debut. Mortality, complication rates, and median hospital stay were higher for patients with missing data on delay compared with the rest of the patients in our study. Thus, inclusion of these patients would have increased the observed effect of delay on outcome. Second, patients with poor prognosis from other reasons than long-standing perforations might be selected toward long treatment delays. Thus, a

Table 4. EFFECT OF DELAY, AGE, YEAR OF PERFORATION, AND ULCER SITE ON OVERALL POSTOPERATIVE COMPLICATION RATE, INFECTIVE COMPLICATIONS, AND GENERAL COMPLICATIONS ACCORDING TO STEPWISE LOGISTIC REGRESSION ANALYSES

Variable	Level	Complications* OR (95% CI)§	General Complications† OR (95% CI)§	Infective Complications‡ OR (95% CI)§
Delay	≤6 hrs	1	1	1
	7–12 hrs	1.34 (0.97–1.87)	1.30 (0.83–2.04)	1.18 (0.74–1.89)
	13–18 hrs	1.50 (0.87–2.58)	1.91 (0.97–3.74)	1.31 (0.60–2.82)
	19–24 hrs	2.75 (1.45–5.20)	2.71 (1.18–6.20)	2.13 (0.87–5.21)
	>24 hrs	5.99 (3.55–10.1)	7.58 (4.13–13.9)	2.99 (1.52–5.85)
Age	<50	1	1	‖
	≥50 years	1.90 (1.38–2.62)	2.00 (1.30–3.07)	
Year	1935–50	1	1	1
	1951–70	0.14 (0.09–0.22)	0.19 (0.10–0.34)	0.14 (0.08–0.23)
	1971–90	0.15 (0.10–0.24)	0.26 (0.19–0.50)	0.12 (0.07–0.20)
Ulcer site	Duodenum	1	‖	1
	Stomach	1.65 (1.06–2.44)		1.90 (1.11–3.24)

* Total number of patients studied were 1096 including 313 cases.
† Total number of patients studied were 933 including 148 cases.
‡ Total number of patients studied were 909 including 124 cases.
§ OR = odds ratio, CI = confidence interval.
‖ Variables were not significant ($p > 0.05$) and not included in final model.

long delay could be a result rather than a cause of poor prognosis. However, this possibility does not correspond with the long-term survival of these patients. If there was a selection of less fit individuals for long delay, the observed survival curve would not approximate the expected curve after the initial divergence, but rather, would follow the slope or diverge even more from the expected curve. We conclude that the most likely overall result of selection bias in this study should be toward underestimation of the effect of treatment delay.

Thus, we will argue that the demonstrated association between delay and outcome is valid. The gradual increase in risk with increasing delay and the magnitude of the observed effects supports the notion of delay as a critical factor for outcome. A causal relationship also is biologically plausible because long-standing perforation usually leads to increased severity of peritonitis and poorer general condition of the patient.

The critical limit from which time delay particularly exerts its negative effect seems to be approximately 12 hours. Recent studies show that duodenal perforations are sterile the first 12 hours and then become contaminated, whereas gastric perforations often are contami-

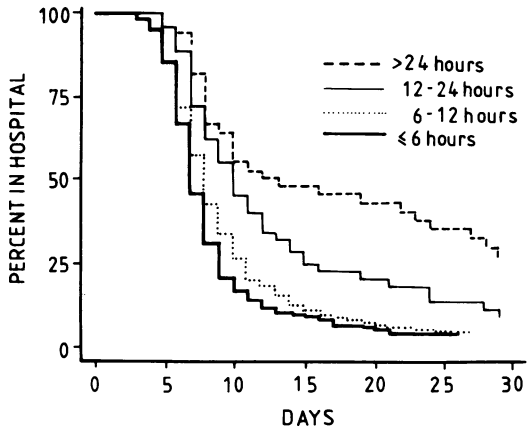

Figure 3. Percent of patients staying in hospital by days after perforation for patients with increasing duration of treatment delay.

Table 5. EFFECT OF DELAY, AGE, YEAR OF PERFORATION, AND ULCER SITE ON RATE OF DISCHARGE FROM HOSPITAL ACCORDING TO COX PROPORTIONAL HAZARDS ANALYSES FOR PATIENTS TREATED 1955–1990

	All Patients		Patients with No Complications	
Variable	Coefficient	p Value	Coefficient	p Value
Delay	−0.0128	<0.001	−0.0043	0.09
Age	−0.0207	<0.001	−0.0200	<0.001
Year	0.0424	<0.001	0.0565	<0.001
Ulcer site*	−0.4152	<0.001	−0.3297	0.01

* Duodenal ulcer = 1, gastric ulcer = 2.

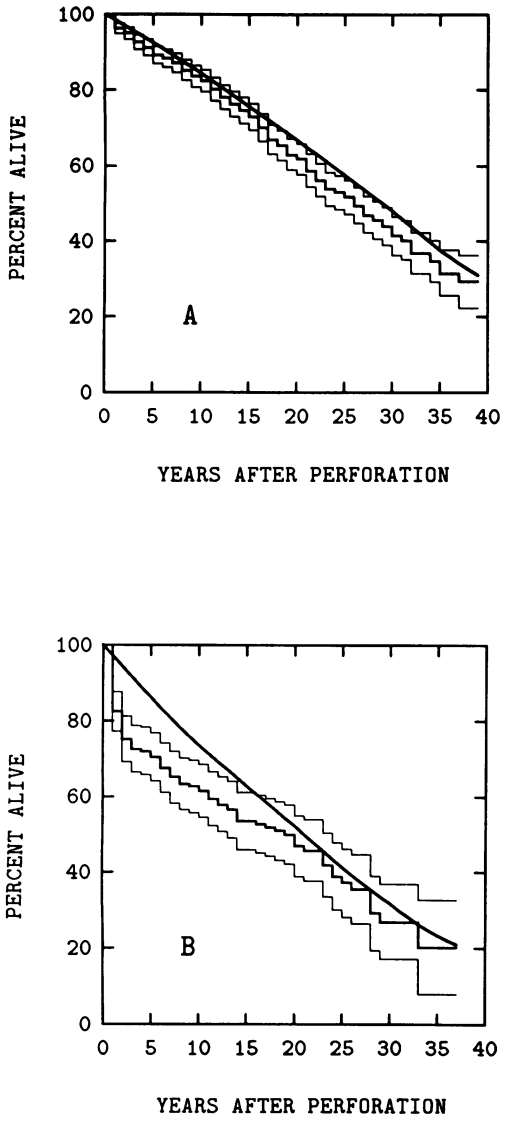

Figure 4. Expected survival (smooth line) and observed survival with 95% confidence bands (stepped lines) by years after ulcer perforation; (A) for patients treated within 12 hours after perforation, (B) for patients treated more than 12 hours after perforation.

nated from the time of the perforation.[25] This may explain why frequency of adverse effects increases when delay exceeds 12 hours and why the increase is more consistent in duodenal than in gastric perforations.

The consequences of long treatment delay are particularly important because delay has been increasing recently.[3] For our patients, median delay increased from 5 hours between 1935 and 1939 to 7.5 hours between 1980 and 1984 and to 9 hours from 1985 to 1990. A similar development can be seen for other countries when comparing older and more recent publications. In the past, delay was generally short, i.e., with median values from 3 to 12 hours,[8-14] with few exceptions.[26] Delay in patients treated after 1970 was higher,[4-6,15,16] although there are some exceptions.[7,27] Fig 1A and Fig 2A show that the additive increase in risk with increasing delay is smaller today than it was 50 years ago. However, the adverse effects when delay exceeds 12 hours are of major importance also the most recent years.

In a previous study, we found a significant decrease in lethality with time when adjusting for related factors.[2] The current detailed analyses show that this decrease occurred during the first years of the study period. We have not been able to find any indication of improvement in lethality or complication rates after 1950 when adjusting for age, ulcer site, and delay.

Treatment delay is a determining factor for survival after ulcer perforation. For patients experiencing very long delays, e.g., because of admittance to a medical rather than a surgical unit, the risk is greatly increased. Thus, the focus should be on the treatment process. Postgraduate training with emphasis on decision making for patients with acute abdominal emergencies probably will have a greater effect on patient survival than any other single measure.

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