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Lethal Pancreatitis

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Thirty-two patients died of pancreatitis and its complications over a 10-year period. Infection (bacteremia, fungemia, or pancreatic abscess) was the major cause of death in 80%. In the remaining 20%, refractory hypotension or respiratory failure were the lethal mechanisms. In only 78% of patients was the correct diagnosis made before death. Ninety-four percent of those who died did so during their first clinical episode of pancreatitis. Prophylactic antibiotics did not prevent the development of pancreatic abscesses and organisms resistant to the antibiotics used often became the primary pathogens. Certain prognostic factors reliably separated those who died from those who lived. Peritoneal lavage and dialysis may be helpful in both the early diagnosis and therapy of severe acute pancreatitis.

INTRODUCTION

"Acute pancreatitis is the most terrible of all the calamities that occur in connection with the abdominal viscera. The suddenness of its onset, the illimitable agony which accompanies it, and the mortality attendant upon it all render it the most formidable of catastrophes" (1).

Acute pancreatitis describes a clinical spectrum ranging from mild, self-limited symptoms of epigastric pain, nausea, and vomiting to an overwhelming, rapidly fatal illness. Biliary tract disease and alcoholism remain the most commonly recognized etiologies (2–4). Biliary tract disease has a mortality of 10–15% while alcoholic pancreatitis has a 1–5% mortality rate (2–6). Mortality is highest (20–40%) in cases occurring postoperatively and in those in which there is no apparent etiology. Overall, a given episode of pancreatitis has an approximate 5–15% mortality, a figure which has remained constant in most reviews over the last 20 years (7–10).

This study was undertaken to examine the clinical course of patients dying with acute pancreatitis. Data were analyzed to assess the modes of presentation, the role of concurrent disease in affecting survival, the actual mechanisms leading to death, the use of antibiotics and their relation to the infectious complications of pancreatitis and whether certain prognostic factors were useful in predicting the outcome of the disease.

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METHODS AND PATIENTS

The hospital records of patients who died with acute pancreatitis were reviewed. Patients were included for evaluation when pancreatitis was the predominant cause of death and when a diagnosis of either diffuse hemorrhagic or necrotizing pancreatitis was made at either surgery or autopsy. Patients were excluded when pancreatitis was not a significant finding at surgery or autopsy. From 1969–1979 there were 32 patients at the University of Michigan Hospitals in whom pancreatitis was the predominant cause of death. Over the same 10-year period, 410 patients had a primary or secondary discharge diagnosis of acute pancreatitis for a mortality rate of 7.8%. An age, sex, and hospital service (medical or surgical)-matched set of 32 patients who had an episode of acute pancreatitis and lived was also studied.

RESULTS

In the group of patients who lived, there were 18 men and 14 women with a mean age of 39 years (range 17–76). The average length of hospitalization was 9 days. Of those who died, there were 18 men and 14 women with a mean age of 49 (range 18–89). The diagnosis of pancreatitis was confirmed at autopsy in 75% and at celiotomy in 25%. Diagnosis was made before death in 78% and at autopsy in the remaining 22%. The average length of hospitalization before death was 51 days. In both groups approximately two-thirds of the patients were on a surgical service and one-third on a medical service. The etiological groups are shown in Table 1.

Serum amylase was measured in 90% of the patients who died. In 20% of these it was normal when first drawn. In both groups of patients the height of the initial amylase was >1000 IU/l in 16 (Table 1). Seven of these instances were in patients with biliary tract disease while only two were in alcoholics. Although the height of the initial amylase may correlate with the presence of cholelithiasis (11), it has never been shown to correlate with prognosis (4, 12, 13).

None of the patients who lived but one-third of those who died were comatose on admission. Seven of these

TABLE 1
Clinical Summary

Etiological Group	No. of Patients		Previous Clinical Pancreatitis		Amylase >1000	
	Lived	Died	Lived	Died	Lived	Died
I. Biliary disease	10	8	4	0	5	2
II. Alcoholism	10	6	7	0	2	0
III. Postoperative	1	6	0	0	1	2
IV. Idiopathic	9	4	3	0	3	0
V. Miscellaneous*	2	8	0	2	0	1
Total	32	32	14	2	11	5

* Miscellaneous causes included severe burns, gunshot wounds, polyarteritis nodosa, systemic lupus erythematosus, hypertriglyceridemia, use of L-asparaginase, and cold water drowning.

TABLE 2
*Isolates from Pancreatic Abscesses (10 Patients)**

E. coli	4
Pseudomonas aeruginosa	3
Klebsiella penumoniae	3
Enterobacter spp.	2
Acinetobacter oxidans	2
Serratia marcescens	2
Proteus spp.	1
Citrobacter spp.	1
Streptococcus fecalis	6
Streptococcus viridans	1
Staphylococcus aureus	1
"Anaerobes"	1
C. albicans	3

* The abscesses were polymicrobial in nine patients.

10 patients were also severely hypotensive. The presence of either an elevated serum amylase or peritoneal signs (rigid abdomen or absent bowel sounds) was helpful in localizing pathology to the abdomen in nine. In the entire series, of the seven patients who did not have the diagnosis made before death, three were unconscious on admission. In one of them an amylase was not measured; in one it was normal; and in one it was elevated and apparently ignored.

Death occurred in the settings of infection, respiratory failure, or renal failure. Infection played a dominant role in the death of 26 (82%) of the 32 patients. Fifteen of these had pancreatic abscesses (diagnosed an average of 18 days after presentation) and the remainder developed either overwhelming bacteremia or fungemia. Subphrenic abscesses were seen in five patients, three of whom also had pancreatic abscesses. Most patients with pancreatic abscesses were also bacteremic with an organism ultimately found in their abscess. Culture results were available for 10 of these patients (Table 2). All but one of these abscesses were polymicrobial. Anaerobes were isolated in only one patient but few anaerobic cultures were obtained. In patients with cholelithiasis and postoperative pancreatitis who died, infection was universally present. Twelve of these 14 patients had pancreatic abscesses and the remaining two had bacteremia. Infection was the cause of death in half of the alcoholic patients and in 75% of patients with miscellaneous or idiopathic causes for their pancreatitis. Only one infectious complication was seen in the patients who lived (a pancreatic abscess developing after cholecystectomy which was drained without complication).

Antibiotics were used in 30/32 (94%) of the patients who died and in 6/21 (29%) of those who lived. They were used in a "prophylactic" sense (empiric therapy on admission without documentation of infection) in more than one-half of the patients in both groups who were given antibiotics. Virtually every antibiotic on the market during the years of the study was used. The most commonly used antibiotics were ampicillin or cephalothin, usually in combination with gentamicin. In the group who died receiving antibiotics empirically, all but one still died of an infectious complication and all of these were with organisms resistant to the original antibiotic choice. Superinfection with *Candida albicans* occurred commonly during antibiotic therapy, being seen as part of the abscess flora in three patients and in the blood of six. In the patients who lived, no fungal superinfection occurred.

An adult respiratory distress syndrome-like picture was seen in almost 20% of the total group. It occurred in patients among all subgroups. The mean time of onset of this complication was 3 days after symptoms began and no cases appeared after 7 days. Arterial hypoxemia (pO_2 <60mm Hg) was present in 50% of all patients who died within the 1st wk of their illness. The six patients who died of adult respiratory distress syndrome all had either acute renal failure or a pancreatic abscess; in fact, half of these six had all three conditions. Thus the lethal respiratory failure seen in this series occurred only with another major complication of pancreatitis.

Renal failure was coexistent with the onset of pancreatitis in four patients and developed in nine of the patients who died. In the group with pre-existing renal failure, one each also had accompanying biliary tract disease, alcoholism, or SLE. The remaining patient had chronic pyelonephritis. Hypotension as an etiology for the renal failure could be clearly demonstrated in six of these nine patients.

Several sets of criteria exist which attempt to predict the clinical outcome (survival or death) of an attack of acute pancreatitis based on an assessment of certain factors early in the course of the disease. Perhaps the best studied are those of Ranson and colleagues (4, 12–14) who evaluated 43 objective findings during the first

48 h of pancreatitis and found 11 predictive of "serious" pancreatitis; *i.e.*, leading to death or requiring >7 days in an intensive care unit (Table 3). In 350 patients with <3 prognostic signs, the mortality was 0.9%. In 100 patients with >3 prognostic signs, mortality increased from 16% in those with three or four signs to 100% in those with seven or eight signs (14). Factors shown to be not predictive of serious illness or mortality were any findings on physical exam or the presence and height of the serum amylase. In this series the mean number of prognostic factors present in those who died was 6.1 (range of 3–9) and in the group who lived a mean of 0.3 (range 0–2; $p < 0.001$ by χ^2). Twenty of the patients who lived had none of these signs present. In the group who died the most common signs were leukocytosis, hypocalcemia, hypoxemia, and decreased renal function.

Therapeutic peritoneal dialysis was attempted in five of the patients who died. In three patients dialysis was administered for renal failure late in their clinical course. Two patients received dialysis as therapy for pancreatitis: one received it 7 days after onset and died 24 h later, and another died shortly after one cycle of dialysis had been given.

DISCUSSION

Previous studies of lethal pancreatitis, comprising 435 cases studied with autopsy since the detailed pathologic study of Fitz in 1889 (15), have underscored several facts observed in this study. The vast majority of patients who die of acute pancreatitis do so during their first clinical episode of the disease. Of 315 patients in the literature for which these data are obtainable (including the current series of 32), 17 (6%) had had a prior clinical attack of pancreatitis. Approximately one-half of the deaths occur in the first few days, usually of hypovolemia or respiratory complications. Those who survive for 1 wk often succumb later to infectious sequelae. From 10–50% of cases are diagnosed on the autopsy table and almost all of these are patients who die within 24–48 h after admission (15–18). These are also the patients most likely to be comatose and have the diagnosis missed (19).

TABLE 3
Ranson Criteria

	Lived (30 Evaluable)	Died (22 Evaluable)
On admission		
Age >55 yr	5	9
Glucose >200 mg/100 ml	0	12
White blood cells >16,000/mm^3	3	16
Lactose dehydrogenase >350 IU/l	0	10
SGOT >250 Sigma-Frankel U/100 ml	1	4
Within 48 h		
Decreased hematocrit by >10%	1	13
Calcium <8 mg/100 ml	4	14
Base deficit >4 mEg/l	0	12
Blood urea nitrogen increase by >5 mg/100 ml	0	17
Fluid sequestration >6 l	0	11
pO_2 <60 mm Hg	0	16

Infection is the overwhelming cause of death in patients surviving beyond 1 wk. A pancreatic abscess is seen in 4–9% of patients with acute pancreatitis with a mortality rate of 25–57%, despite advances in diagnosis, aggressive surgical management, and antibiotic therapy (20–23). Possible routes of infection include invasion from infected bile, direct penetration through the wall of the transverse colon, and hematogenous or lymphatic spread (2). In approximately half, the abscesses are polymicrobial although in this study 10/11 (91%) had multiple organisms. Most series were compiled before the advent of current anaerobic technology but one report found Bacteroides spp. in 15% of cases (22). Enterobacteriaceae predominate with *Escherichia coli* and Klebsiella seen most frequently. *C. albicans* is seen only in well-established abscesses and probably represents superinfection due to prior antibiotic therapy.

The controversy over the use of prophylactic antibiotics during acute severe pancreatitis has not been settled. One retrospective (24) and three prospective studies comprising over 700 patients have compared outcome in patients given prophylactic ampicillin (25, 26) or cephalothin (24, 27) and found no difference in morbidity or mortality. However, virtually all of the patients in these studies were alcoholics with mild pancreatitis, a group expected to have the lowest mortality.

Should a pancreatic abscess develop, mortality is highest (80–85%) in those patients with biliary tract disease or postoperative etiologies (6). Most patients in these groups, however, are already receiving antibiotics. Indeed, in the patients who died, half were already receiving antibiotics at the time that an ultimately fatal infectious complication developed. Organisms (bacterial or fungal) that were subsequently recovered from the blood or abscesses in these patients were uniformly resistant to the antibiotics initially used. The subgroup with biliary tract disease may be one in which prophylactic antibiotics would deserve a trial, since their mortality is so high if infection does occur. At present, however, there is no good data to support the use of prophylactic antibiotics in acute pancreatitis, especially in patients who are not critically ill on presentation.

The adult respiratory distress syndrome occurred in 20% of those dying. All six of these patients died, which is a higher mortality from this process than that previously reported (28). However, a similarly high mortality from respiratory failure in alcoholics with acute pan-

creatitis has been observed (16, 27). These six patients all had at least one other major metabolic process, such as renal failure or infection, which may have directly contributed to this higher mortality.

Pancreatitis has been reported to occur at a higher rate in patients with pre-existing renal failure (3). In this series, however, three of four such patients had another associated condition such as alcoholism. Oliguric renal failure is not uncommon in acute pancreatitis, especially in the first 24–48 h after presentation. Hypovolemia as a cause of renal failure could account for six of nine such instances in this study. However, in three of these nine and in at least 18 other patients described in the literature (29, 30), hypotension could not be documented (although perhaps not detected) and some other factor, such as a circulating vasopressor having selective renal activity, has been postulated to cause acute renal failure (2, 31).

Several attempts have been made to predict the clinical severity of a given episode of acute pancreatitis. The studies of Ranson and colleagues (4, 12–14) did not find predictive utility from any parameters on physical exam, while others have (32). This study also illustrated the use of Ranson's criteria in predicting a high risk group of patients with those living having a mean of 0.5 prognostic factors while those dying had 6.1.

There has been recent interest in the role of peritoneal lavage and dialysis in both the diagnosis and therapy of acute pancreatitis early in its course. Diagnostic peritoneal lavage (considered positive if more than 10 ml of free peritoneal fluid was obtained or any lavage return with a dark color) was found as predictive of the subsequent clinical course as a clinical grading scheme or the criteria of McMahon *et al.* (33). A randomized trial of therapeutic peritoneal lavage in 70 patients thought to have severe alcoholic pancreatitis (hypocalcemia, acidosis, hypotension, hypoxemia) found "improvement" at 24 h and less mortality in the group dialyzed (27). An earlier report of Ranson and Spencer (34) showed a dramatic reduction in the early mortality of pancreatitis in patients given 48 h of peritoneal dialysis. However, late mortality (almost all due to pancreatic abscesses) was unaffected. These studies have thus suggested at least improved early survival in those patients supported with peritoneal dialysis and it may deserve a wider role in diagnosis and therapy than it currently has.

Since virtually all patients who die of acute pancreatitis do so during their first clinical episode of the disease (regardless of etiological subgroup), particular attention to their changing physiology and the appearance of prognostic factors should be assessed early in the clinical course. Serum amylase, although not predictive, is a useful screening device and may have particular utility in unconscious patients, as their pancreatitis is often diagnosed postmortem (19). The role of prophylactic antibiotics has not been clarified in severely ill patients, but if proven beneficial, may offer a means of diminishing the late mortality from infection (especially in patients with biliary tract pathology). The role of peritoneal lavage and dialysis in the early diagnosis and therapy of severe pancreatitis deserves further study.

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