

Acute Pancreatitis:

Analysis of Factors Influencing Survival

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Of patients with acute pancreatitis (AP), there remains a group who suffer life-threatening complications despite current modes of therapy. To identify factors which distinguish this group from the entire patient population, a retrospective analysis of 519 cases of AP occurring over a 5-year period was undertaken. Thirty-one per cent of these patients had a history of alcoholism and 47% had a history of biliary disease. The overall mortality was 12.9%. Of symptoms and signs recorded at the time of admission, hypotension, tachycardia, fever, abdominal mass, and abnormal examination of the lung fields correlated positively with increased mortality. Seven features of the initial laboratory examination correlated with increased mortality. Shock, massive colloid requirement, hypocalcemia, renal failure, and respiratory failure requiring endotracheal intubation were complications associated with the poorest prognosis. Among patients in this series with three or more of these clinical characteristics, maximal nonoperative treatment yielded a survival rate of 29%, compared to the 64% survival rate for a group of patients treated operatively with cholecystostomy, gastrostomy, feeding jejunostomy, and sump drainage of the lesser sac and retroperitoneum.

ACU TE PANCREATITIS presents a broad clinical spectrum ranging from cases so mild that symptoms abate before the diagnosis is actively pursued, to cases which progress rapidly to multisystem failure and eventual demise of the patient despite current modes of therapy. The great majority of cases fall somewhere between these two extremes, and most patients respond to conservative therapeutic measures including nasogastric suction and intravenous fluid replacement. This present study

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was undertaken to examine the clinical spectrum of acute pancreatitis and to look in particular at that group of patients who suffer life-threatening complications. The early identification and subsequent management of these high risk patients are two areas of active controversy. In this retrospective study, information which is available to the clinician seeing a patient with a possible diagnosis of acute pancreatitis was analyzed with respect to diagnostic and prognostic value. Clinical and laboratory data were evaluated as to their usefulness in the early identification of patients who can be expected to respond poorly to conservative measures, and who might benefit from any of several new therapeutic modalities under evaluation at this and other centers.

Methods and Materials

Population. Five hundred forty-three patients with a clinical diagnosis of acute pancreatitis were treated on the surgical and medical services of the Massachusetts General Hospital during the period from December 1963 through April 1969. Of these, 24 had undergone a surgical operation during the 60-day period prior to diagnosis or admission and were presumed to represent postoperative pancreatitis. The remaining 519 patients with acute pancreatitis constitute the patient population

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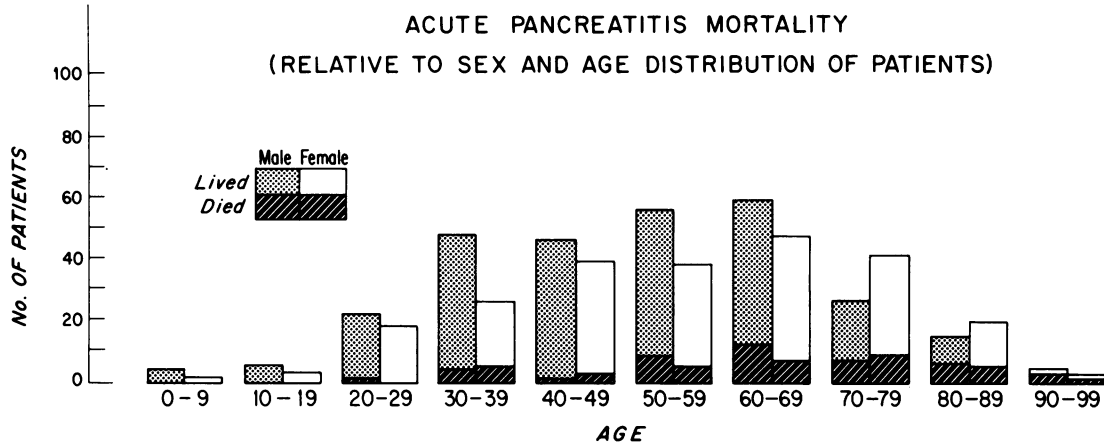


FIG. 1. The overall mortality is 12.9%. Increased age is associated with increased mortality among both males and females.

analyzed in this study. This group includes 285 men and 234 women. The youngest patient was 5 years old at the time of diagnosis and the eldest was 94. The mean age for the total population was 53.8 years.

Data Base. These 519 patients' hospital records were reviewed with particular attention to an extensive list of historical information, physical findings, laboratory data, and specifics regarding hospital course and complications. The facts were then catalogued by standard key-punch technique, coded, and stored on magnetic tape. Processing and statistical analysis were carried out on an IBM 370/168 computer at the Harvard University Center for Information Technology, Cambridge, Massachusetts. Statistical significance of results was determined routinely by using the Chi Square test. This

test was replaced by the Fisher Exact test when indicated because of small numbers.

Results

Mortality. The overall mortality for the entire series was 12.9% (Fig. 1). The mortality for males (13.4%) was not significantly different from that for females (12.4%). Among males, the mortality for patients over 60 years of age was significantly greater than that of the total population. Among females, this was true of patients over 70 years of age. Figure 1 illustrates the association of increased mortality with increased age, a trend which is consistent for the male and female populations as well as the total group.

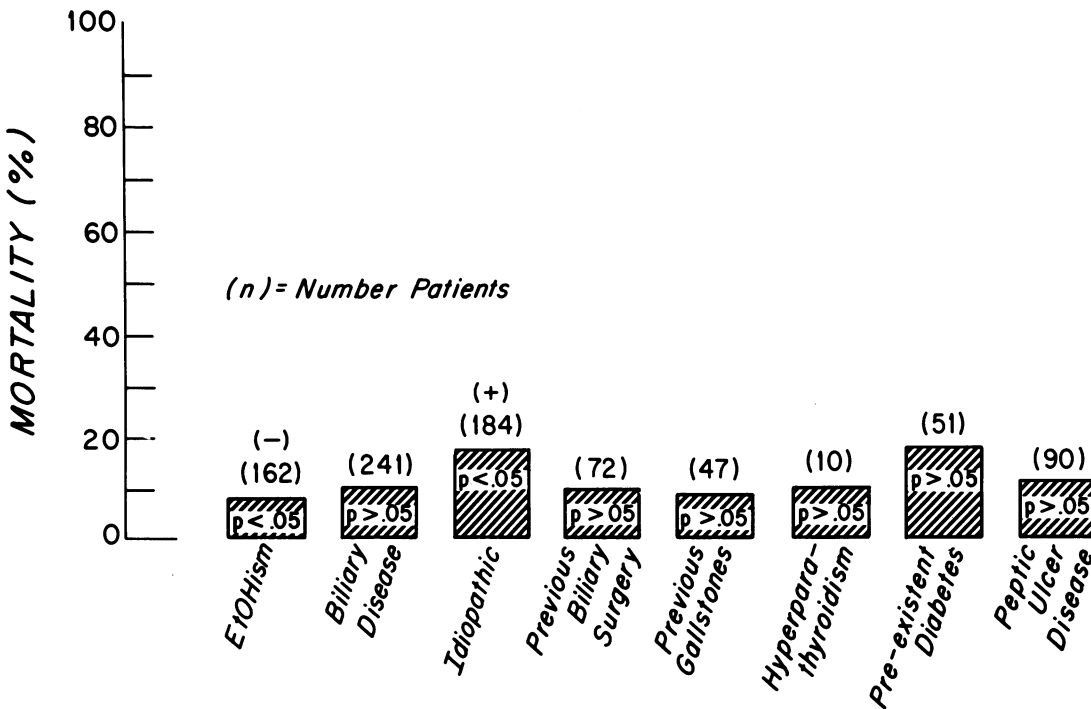
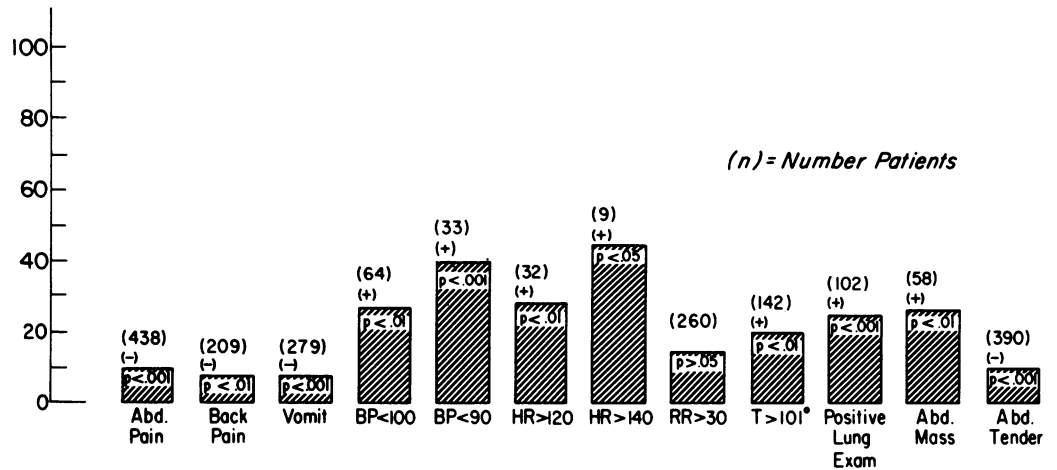


FIG. 2. Etiologic factors. Mortality of patients with idiopathic pancreatitis is significantly greater than that of patients with alcoholism and/or previous biliary disease. (See text for discussion).

FIG. 3. Admission history and physical exam. At the time of admission, findings of systolic hypotension, tachycardia, fever, abnormal examination of the lungs and presence of an abdominal mass were associated with significantly increased mortality.



The mean duration of hospitalization for the total population was 16.7 days and was greater for males (19.6 days) than for females (13.1 days).

Causation. Figure 2 illustrates the mortality rate relative to etiologic factors. One hundred and sixty-two patients, 31.2% of the total population, had a history of alcoholism. Two hundred and forty-one patients, 46.4% of the total population, had a history of biliary disease. Of these latter patients, 47 had pre-existent gallstones, and 72 had undergone biliary surgery more than 60 days prior to diagnosis. Sixty-eight patients had positive histories for both alcoholism and biliary disease. The 184 patients whose histories were positive for neither alcoholism nor previous biliary disease were considered to have idiopathic acute pancreatitis. The mortality for this idiopathic group (17.4%) was significantly higher than for those with alcoholism (8.0%) and for those with previous biliary disease (10.0%). Thus, alcoholism correlated negatively with mortality ($P < .05$), and a history of biliary disease had no significant correlation. Failure to be classified into either of these groups, i.e. idiopathic acute pancreatitis, had a positive correlation with mortality ($P < .05$).

Of the 519 patients, 10 had hyperparathyroidism, 51 had pre-existing diabetes, 90 had a history of peptic ulcer disease, and 23 had a history of hematemesis. None of these four groups showed a mortality rate significantly different from the overall series. None of the above mentioned etiologic factors was associated with a duration of hospital stay significantly different from the mean.

Examination on Admission. The mortality rate relative to features in the history obtained at the time of admission and findings in the initial physical examination is illustrated in Fig. 3. Vomiting (279 patients), abdominal pain (438 patients) and back pain (209 patients) were all associated with mortality rates no higher than that for the total population. Among the vital signs, low systolic blood pressure, tachycardia and elevated temperature

all correlated in a positive fashion with death rate. Tachypnea did not correlate with mortality, although an abnormal examination of the lung fields was associated with a significantly increased mortality ($P < .001$). A palpable mass in the abdomen, whether identified as organomegaly or not, was associated with significantly increased mortality ($P < .01$). Abdominal tenderness, present in 390 patients, correlated with a decreased mortality ($P < .001$), and was present more frequently in young patients than in the older age groups. Grey-Turner's sign (5 patients) and Cullen's sign (4 patients) were associated with increased mortality (60% and 50% respectively), but only the former was statistically significant ($P < .05$), because of the small sample. No elements of the admission history and physical examination were associated with significant prolongation of hospital stay among patients who survived and were discharged alive.

Laboratory Examination. Table 1 lists 12 laboratory tests (hematology and blood chemistry) that were analyzed to determine their prognostic value. Analysis of available test results was conducted for three time periods as follows: 1) on admission and during first hospital day; 2) on admission and during the first two hospital days; 3) entire period of hospitalization.

In the first time period, a total of seven features in the laboratory examination correlated positively with increased mortality ($P < .05$). These are: minimum serum albumin less than 3 gm/100 ml, maximum prothrombin time greater than 14 seconds, maximum white blood cell count greater than 20,000 per mm^3 , maximum hematocrit less than 30%, maximum serum creatinine greater than 2 mg/100 ml, maximum blood urea nitrogen (BUN) greater than 30 mg/100 ml, and maximum serum bilirubin (total) greater than 4 mg/100 ml.

Two additional features of the laboratory examination attain a significant level of correlation with mortality when considered over the second time period, i.e. the first 48 hours of hospitalization. These are a minimum

TABLE 1. Prognostic Value of Laboratory Examinations: Correlation with Mortality

		Admission and first hospital day	Admission and first two hospital days	Entire hospital course
Amylase max.	≤25 Russell U./ml	(38, 18.4%)	(56, 19.6%)	(3, 0.0%)
Amylase max.	>25 Russell U./ml	(352, 11.4%)	(405, 11.9%)	(516, 13.0%)
Prothrombin time max.	>14 seconds	(88, 28.4%)‡	(105, 25.7%)‡	(173, 26.0%)‡
WBC max.	>20,000/mm ³	(62, 22.6%)*	(79, 24.1%)†	(116, 26.7%)‡
Hematocrit max.	≤30%	(13, 38.5%)*	(14, 42.9%)†	(8, 37.5%)
Hematocrit max.	≥50%	(24, 25.0%)	(31, 22.6%)	(42, 21.4%)
Hematocrit min.	≤30%	(21, 23.8%)	(27, 29.6%)*	(72, 26.4%)‡
Hematocrit min.	>50%	(13, 23.1%)	(6, 33.3%)	(5, 20.0%)
Creatinine max.	>2 mg/100 ml	(13, 53.8%)†	(22, 50.0%)‡	(44, 54.5%)‡
Calcium min.	≤8 mg/100 ml	(26, 15.4%)	(56, 19.6%)*	(136, 22.1%)‡
Calcium min.	≤7 mg/100 ml	(10, 20.0%)	(18, 27.8%)*	(34, 29.4%)†
Calcium min.	≤6 mg/100 ml	(3, 33.3%)	(7, 14.3%)	(14, 28.6%)
BUN max.	>30 mg/100 ml	(45, 48.9%)‡	(53, 49.1%)‡	(98, 49.0%)‡
BUN max.	>40 mg/100 ml	(30, 53.3%)‡	(37, 54.1%)‡	(70, 60.0%)‡
Bilirubin max.	>4 mg/100 ml	(43, 23.3%)*	(59, 23.7%)†	(80, 28.8%)‡
Albumen min.	<3 gm/100 ml	(9, 44.4%)*	(14, 35.7%)*	(47, 36.2%)‡

Figures in parentheses represent number of patients with indicated test result, followed by per cent mortality for these patients.

* Significant positive correlation with mortality P < 0.05 Fisher's Exact Test; † Significant positive correlation with mortality P < 0.01 Fisher's Exact Test; ‡ Significant positive correlation with mortality P < 0.001 Fisher's Exact Test.

hematocrit less than or equal to 30%, and a minimum serum calcium less than or equal to 8 mg/100 ml. A minimum serum calcium less than or equal to 7 mg/100 ml also attains a significant correlation with death rate and is associated with a higher mortality than is the 8 mg/100 ml level (27.8% vs. 19.6%).

As indicated in Table 1, all those features of the laboratory examination that attain a significant level of correlation with mortality at anytime during the patient's entire hospitalization (period III), have attained significance (P < .05) by the end of the first 48 hours. The individual prognostic accuracy of features of the laboratory examination during this time period is illustrated in Fig. 4.

The features of the laboratory examination which were analyzed and found not to correlate with mortality were minimum and maximum levels of serum amylase (Fig. 5), maximum serum lipase, maximum alkaline phosphatase, and minimum arterial Po₂. It should be noted, however, that due to the timing of the study (hospital admissions

between 1962 and 1969) blood gas determinations were not available in a sufficient number of patients during the first 48 hours to allow a significant analysis of these variables relative to mortality.

Five elements of the laboratory examination were associated with significant prolongation of hospital stay among patients who survived and were discharged live. As shown in Fig. 6, these are minimum serum albumin less than 3 gm/100 ml, minimum hematocrit less than 30%, maximum serum creatinine greater than 2 mg/100 ml, minimum serum calcium less than 8 mg/100 ml, and maximum blood urea nitrogen (BUN) greater than 30 mg/100 ml.

Roentgenographic Findings. One hundred seventy-eight patients, 34.3% of the total population, had at least one chest x-ray which was interpreted as abnormal at some time during their hospital course. Forty-one of these patients died (23.0%). Thus, an abnormal chest x-ray correlated strongly (P < .001) with mortality. One

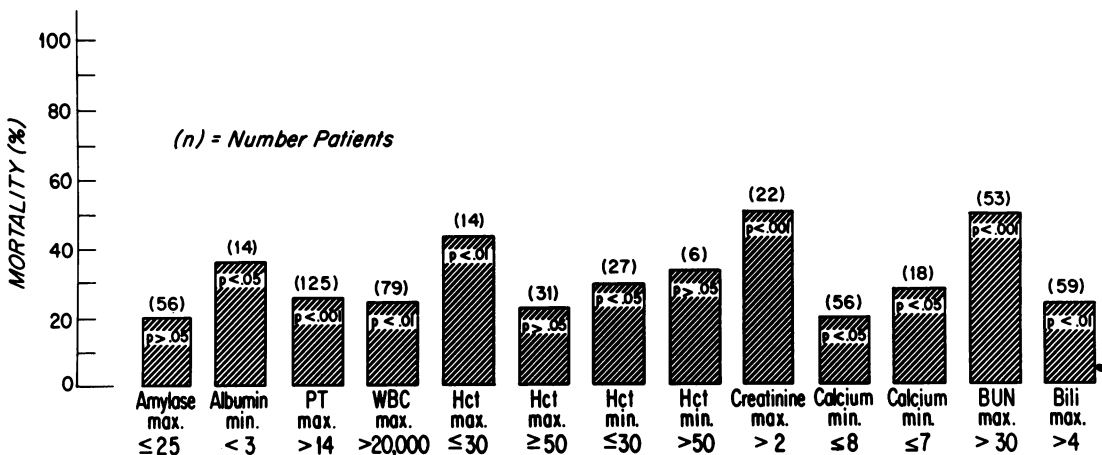


FIG. 4. Correlation of mortality (%) with abnormalities of the laboratory examination during the first 48 hours of hospitalization.

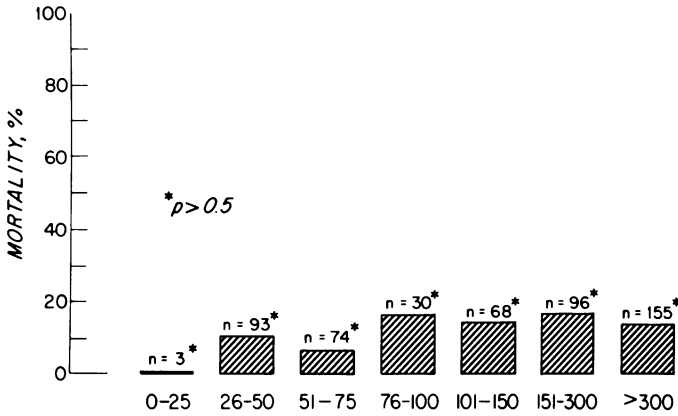


FIG. 5. Maximum level of serum amylase during hospitalization does not correlate with mortality.

hundred and sixty-four patients underwent a Graham-Cole test (oral cholecystography). Forty-six per cent of these were interpreted as abnormal. Such findings did not correlate with mortality.

Four hundred and twenty-three patients underwent plain film examination of the abdomen. Thirteen patient's films showed loss of the psoas shadow, and 9 showed pancreatic calcification. Neither of these findings correlated with mortality.

Hospital Course and Complications. The mortality rate relative to complications suffered by 10 or more patients in this series is shown in Fig. 7. Twenty-three patients suffered acute renal failure. Only one survived. While elevations of both the BUN and serum creatinine levels correlated with mortality (Table I), there was no correlation between death rate and reduced urine output (of 400 cc or less) in the first 24 hours of

hospitalization. This observation suggests that early urine output may better reflect the degree of hydration and/or cardiac output than the status of renal function in patients with acute pancreatitis.

Forty-eight patients required tracheal intubation and 44 required mechanical ventilatory assistance. These factors were associated with 79.2% and 75.0% mortality respectively. A clinical impression of hemorrhage from any source (which is to be distinguished from the classification hemorrhagic pancreatitis referred to by others) was associated with a 75% mortality rate. In this series, 19 patients had a diagnosis of upper GI hemorrhage, 3 patients had a diagnosis of intraperitoneal bleeding, and 5 patients suffered a generalized bleeding diathesis. Of the 28 patients with a diagnosis of hemorrhage, 8 had a prothrombin time of greater than 14 seconds during the first 24 hours of hospitalization. All 8 of these patients subsequently died.

Thirty-three patients presented initially with a systolic blood pressure of less than 90 mm Hg and 47 had similarly low pressures during the first 24 hours. Mortality rates for these two groups were 39.4% and 29.8% respectively ($P < .001$). Sixty-four patients presented initially with systolic blood pressure of less than 100 mg Hg. Twenty-nine per cent of these patients died.

Fifty-two patients had positive blood cultures, and 38.5% of these died. Thirteen patients had a clinical diagnosis of septic shock (mortality 84.6%) but only 7 of these patients' charts had laboratory reports of positive blood cultures. Three hundred and sixty-three patients received antibiotics, and, while this factor correlated positively with mortality ($P < .001$), this information must be regarded cautiously, given the variable and subjective criteria for initiating antibiotic therapy

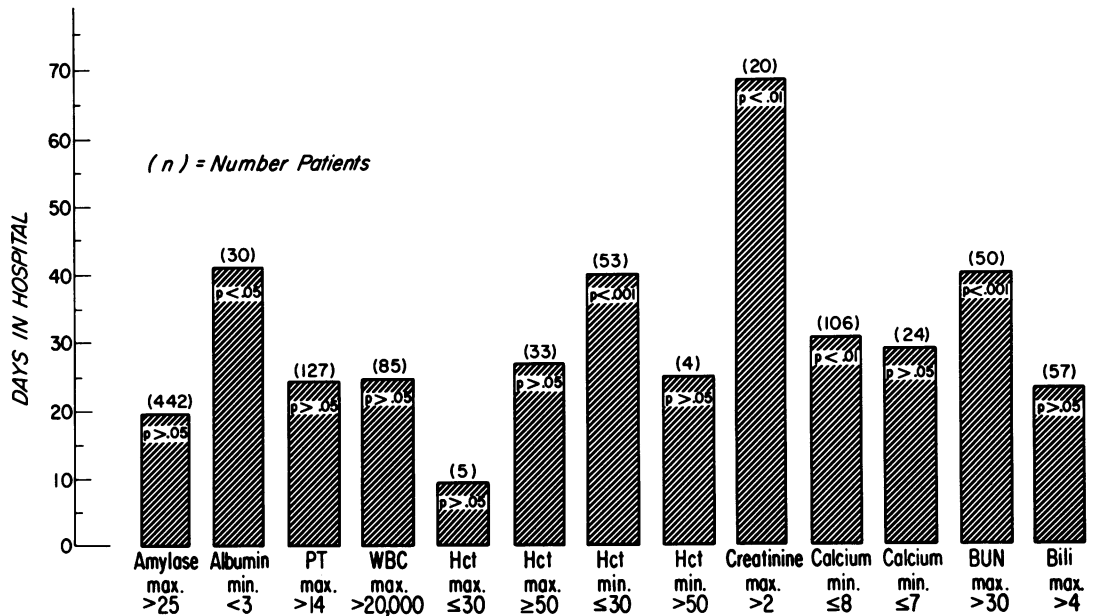


FIG. 6. Prognostic value of laboratory examinations. Correlation of 5 abnormalities of the laboratory examination with increased duration of hospital stay among patients who survived and were discharged.

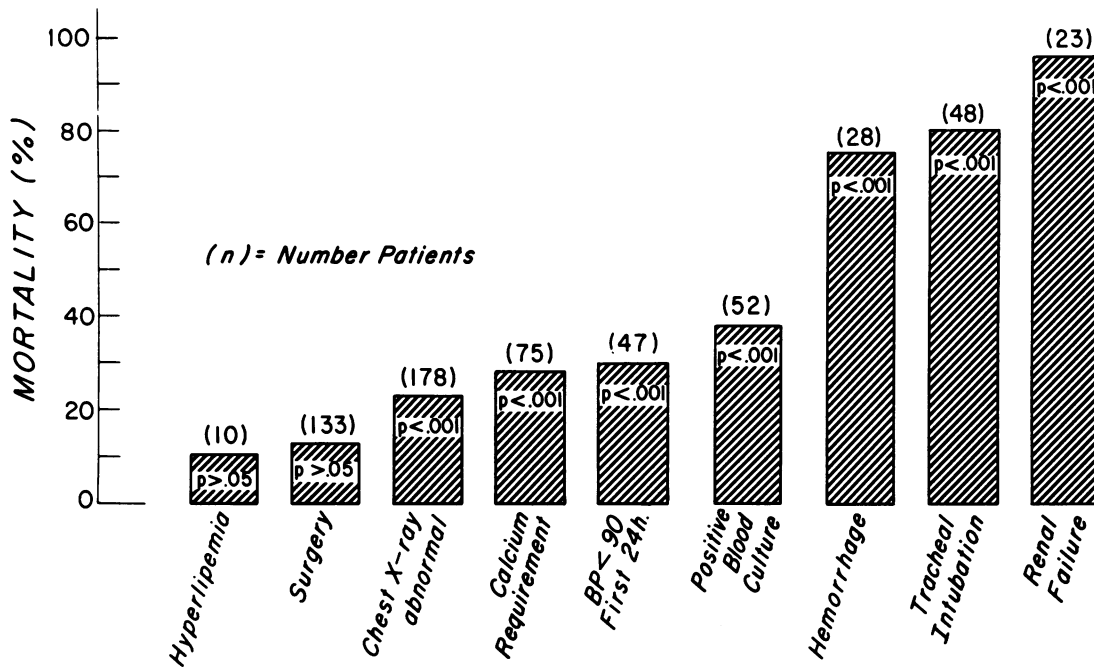


FIG. 7. Mortality rate relative to complications suffered by ten or more patients.

and the tendency to use antibiotics empirically in the more severe cases.

Calcium requirement, another subjective evaluation, also correlated with mortality ($P < .001$). Seventy-five patients were thought to require calcium and of these 28% died. Only two patients suffered tetany; both died. Ten patients had a diagnosis of hyperlipemia, based on lacescent serum or an elevated serum lipid determination. Mortality in this group did not differ from that of the total population.

The 133 patients who underwent a surgical operation at any time during their hospitalization had a mortality rate that was the same as that of the total population. Of the total population, 10 patients developed pancreatic cysts and 18 developed abscesses. Neither of these complications correlated with increased mortality.

Table 2 shows the mortality rate relative to the extent of colloid replacement. In each time period, there is a positive correlation of quantity of colloid given with mortality. Once again, the usefulness of this data is

tempered by the subjective nature of a judgement of colloid requirement.

During hospitalization, five patients developed diabetes, defined as prolonged hyperglycemia; two died.

Discussion

The 12.9% mortality rate for acute pancreatitis at the Massachusetts General Hospital during the 5-year period 1963–1969 is similar to figures in recent reports from other centers.^{21,25} It is also similar to the 11% figure reported from the Massachusetts General Hospital by Bartlett and Nardi for the 5-year period 1949–1953.³

The patient population analyzed in this study is that of a university teaching hospital which draws upon the heavily populated urban area in which it is located, but which also serves as a referral center for a wide area. These factors and the fact that the data analyzed herein were obtained by review of hospital charts, are possible explanations for the higher percentage of “idiopathic pancreatitis” than that reported by other authors.

TABLE 2. Mortality Rate Relative to Amount of Colloid Administered

	Day 1		Day 2–3		Day 4–7		Week 1–2		Beyond Week 2	
	n	% mort	n	% mort	n	% mort	n	% mort	n	% mort
0–1000 cc	86	18.6%	115	13.9%	68	23.5%	45	26.7%	27	22.2%
1001–2000 cc	19	26.3%	34	29.4%	21	23.8%	14	21.4%	5	20.0%
>2000 cc	12	75.0%	18	38.9%	9	44.4%	21	42.9%	33	51.5%
	P < .001		P < .001		P < .001		P < .001		P < .001	

Acute pancreatitis favors neither sex, with regard to incidence or mortality. Increased age was associated with an increased death rate, as reported by others.^{2,13,17,21}

Early Prognostic Signs

Physical Signs. Identification of the severely threatened patient with acute pancreatitis begins with the initial phase of the examination, and the recording of vital signs. Hypotension, tachycardia and fever upon presentation were all associated with increased mortality. Foster and Ziffren¹¹ reported a high mortality of 86.9% in a group of 23 patients with acute pancreatitis and shock. Facey et al.,⁹ Elliot,⁸ and Ranson,²¹ all reported that in most instances, hypotension did not persist in the face of vigorous intravenous replacement. In our series, however, there was a greater than 39% mortality among the 33 patients who presented with a systolic blood pressure of less than 90 mm Hg, and a 29% mortality among the 64 patients who presented with systolic blood pressure of less than 100 mm Hg, though the usual measures were taken to correct hypovolemia. The importance of a high index of suspicion to rule out acute pancreatitis in the moribund patient with hypotension is demonstrated. Eight of the 25 fatal cases of acute pancreatitis in the series reported by Toffler and Spiro²⁴ presented with shock or coma, and no diagnosis was made before death.

Black⁴ reported fever as a presenting sign in 75% of a group of 250 patients with acute pancreatitis. In the present series, 142 patients (27%) had an initial temperature greater than 101°F and 20% of these patients died.

Of the remainder of the physical examination, the presence of an abdominal mass and abnormal findings over the lung fields correlated with increased mortality. Our results suggest that in acute pancreatitis the initial physical findings do in fact help to predict the severity of the clinical course, though little importance has in the past been placed upon their prognostic value.

Serum Amylase. All but three of the 519 patients had a serum amylase greater than 25 Russell units¹⁶ recorded at some time during their hospital course. For the 56 patients who had a normal serum amylase (0–25 Russell units) recorded during the early part of their hospitalization, the mortality rate was 20%, which appears greater than that for the overall group, but was not statistically significant. Albo and Silen² reported a normal value for the serum amylase in one-third of their very ill patients with hemorrhagic pancreatitis.

The maximum amylase in the first 48 hours and in the entire hospital course did not appear to be of prognostic value. This observation confirms previous reports by

Bockus,⁵ Pollack,²⁰ Trapnell,²⁵ Edmonson,⁷ and Ranson.²¹ Our data do not corroborate the report by Adams and his group¹ in which the serum amylase level was inversely related to the severity of the disease. The prognostic value of persistence of elevated amylase levels, which was reported by Foster and Ziffren,¹¹ Bockus,⁵ and Veith,²⁶ and which Trapnell²⁵ failed to demonstrate, was not evaluated in this study. In the present series of patients, however, the maximum level of amylase at any time during the hospital course was no better indicator of the severity of disease than were similar values obtained during the initial 48 hours.

White Blood Cell Count. Thal,²³ and Silen,² and Ranson and colleagues²¹ have all reported a positive correlation between leukocytosis and severity of disease. Of the 519 patients in this series, 79 had a white blood cell count greater than 20,000 per mm³ during the first 48 hours. Mortality for this group was 24% which is significantly greater than that for the total population ($P < .01$).

Hematocrit. A hematocrit of less than 30% at any time during the initial 48 hours correlated with increased mortality ($P < .05$). Failure to elevate the hematocrit above the 30% level during the same time period was associated with a 43% mortality ($P < .01$). Thus, the presence of anemia was a useful prognostic sign and the importance of early treatment by transfusion with whole blood or packed red blood cells is also demonstrated. Our data do not confirm the report by Gray and Rosenman¹⁴ that hemoconcentration on admission is significant as a poor prognostic sign.

Respiratory Insufficiency. Abnormal examination of the lung fields, by both physical and roentgenographic methods correlated with increased mortality in patients in this series. The importance of diagnosing respiratory insufficiency early, however, requires a high index of suspicion and confirmation by determination of arterial blood gases.⁶ Ranson²² reported a high incidence of mild to moderate respiratory insufficiency based on arterial blood gas determinations in a group of patients among whom very few had clinically or roentgenographically apparent signs of respiratory problems. Fishbein and colleagues¹⁰ and Lawson et al.¹⁸ noted earlier the relation between respiratory complications and poor prognosis in acute pancreatitis. Warshaw and colleagues recently reported a series of 7 patients with severe pancreatitis and a distinct form of pulmonary injury characterized by disruption of the alveolar-capillary membrane, leading to pulmonary edema.²⁸ In these cases, oxygenation and ventilatory function improved during a period of controlled ventilation with positive end-expiratory pressure. It should be emphasized that this particular type of pulmonary injury is not shared by all or even most patients with acute pancreatitis compli-

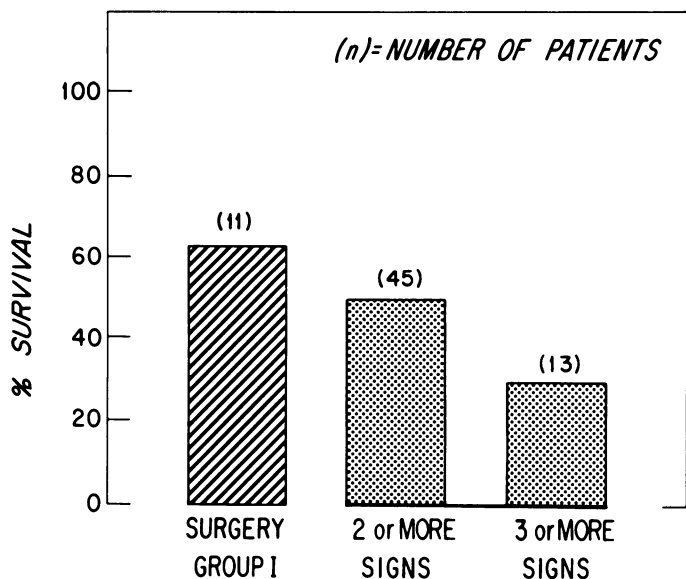


FIG. 8. Survival of patients with shock, respiratory failure, hypocalcemia and massive colloid requirement. Comparison of survival of severely ill patients undergoing cholecystostomy, gastrostomy, feeding jejunostomy and sump drainage of the lesser sac and retroperitoneum (Group I)²⁷ to that of comparably ill patients in the present series who did not undergo that operation.

cated by respiratory insufficiency. Forty-eight patients in the present series had respiratory complications necessitating endotracheal intubation which was associated with a mortality rate of nearly 80%. Perhaps earlier and more effective intervention in the present era will reduce this figure.

Renal Function. Many authors have reported the incidence of altered renal function in the presence of acute pancreatitis. In this series, elevations of both the BUN (to greater than 30 mg/100 ml) and the serum creatinine (to greater than 2 mg/100 ml) were associated with significant increases in the mortality rate. Frey¹² reported an 80% mortality rate for patients with acute pancreatitis who suffered acute renal failure. Of the 23 patients in this series who suffered frank renal failure, only one survived (96% mortality). As noted above, in the patients under discussion, oliguria during the initial 24 hours is not a reliable indication of renal failure.

Howard and Jordan,¹⁵ Pollack,²⁰ Nardi¹⁹ and Trapnell²⁵ all have pointed out that exploratory laparotomy does not necessarily increase the mortality of acute pancreatitis. Of the 519 patients in this series, 133 underwent surgery and had a mortality rate that was the same as that for the total population.

The aforementioned studies do not selectively address the question of surgical treatment of those severely ill patients with acute pancreatitis who continue to deteriorate despite maximal medical treatment. These patients might benefit from any of several therapeutic modalities currently under evaluation. These include

peritoneal lavage, subtotal pancreatectomy, and the use of anti-enzyme preparations. Lawson and Daggett and their associates¹⁸ advocated for such patients on operation that includes cholecystostomy, gastrostomy, feeding jejunostomy, and sump drainage of the lesser sac and retroperitoneum. Warshaw and colleagues²⁷ undertook a retrospective analysis of patients so treated to identify those most likely to benefit from such a procedure. Group 1 of their study consisted of 11 patients with acute pancreatitis judged to be dying. All but one of them had at least two, and most had three or four of the following clinical characteristics: 1) respiratory failure requiring intubation; 2) shock; 3) massive colloid requirement; and 4) serum calcium of 8.0 mg/100 ml or less. Seven of the 11, (64%), survived and were followed for an average of two years. In the present series, the survival rate for all patients with three or more of those same clinical characteristics was 29% (Fig. 8). For patients with two or more of those clinical characteristics, the survival rate was 51%. The high mortality of such severely ill patients, despite maximal medical treatment, suggests that alternative therapeutic approaches receive broader consideration.

Conclusions

A retrospective analysis of 519 cases of acute pancreatitis was undertaken. Clinical and laboratory examinations were analyzed to determine their prognostic value. Hypotension, tachycardia, fever, and abnormal lung findings correlated with increased mortality. The degree of elevation of the serum amylase was not useful prognostically. Certain laboratory tests could be used to select more severe degrees of pancreatitis during the initial 48 hours, as evidenced by higher mortality rates. Those features associated with an exceedingly poor prognosis have been identified. High risk patients may benefit from early surgical intervention.

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