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ORIGINAL ARTICLE

Mortality in Acute Pancreatitis: Is It an Early or a Late Event?

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ABSTRACT

Context Many prior studies have suggested that the majority of deaths in severe acute pancreatitis occur late in the course of the disease as a result of pancreatic sepsis or pancreatic septic-like syndrome. Other have observed that at least half of the deaths occur early as a result of multisystem organ failure.

Objective The aim of the present study was to determine the timing of mortality of severe acute pancreatitis and to analyze the course of the disease in a large series of patients.

Patients All consecutive patients with a diagnosis of acute pancreatitis admitted to our Centre from October 1984 to December 2000 were retrospectively studied. One thousand one hundred and fifty episodes of acute pancreatitis occurred in 1,135 patients.

Main outcome measures Total mortality and frequency of early deaths (less than or equal to 14 days after admission). The clinical features of patients who died were also compared in the early and late mortality groups.

Results The overall mortality rate of acute pancreatitis was 4.8% (55 deaths out of 1,135 cases) and when considering the severe forms only, it was13.5% (55 deaths out of 408 cases); 28 deaths (50.9%) occurred within the first two weeks of hospitalization (median day 8, range 2-14) whereas 27 cases (49.1%) occurred after two weeks (median day 28, range 15-56). Early deaths resulted primarily from multisystem organ failure; late deaths occurred mainly from complications in patients having infected necrosis.

Conclusion Early deaths in severe acute pancreatitis occur in the half of patients within the first 14 days owing to multi-organ system failure. The remainder of deaths occur later from complications secondary to the infection of pancreatic necrosis; in this subgroup of patients, the association of infected necrosis with organ failure is found frequently.

INTRODUCTION

Recent knowledge regarding the natural history and pathogenesis of severe acute pancreatitis has brought to light to the concept, that in the vast majority of patients, the disease progresses in two phases. The first two weeks are characterized by a systemic inflammatory response syndrome with secondary multi-organ failure (MOF) owing to the release of various cytokines [1, 2]. Later, the outcome may be complicated by the infection of pancreatic and peripancreatic necrosis and secondary MOF [3]. Accordingly, two peaks in mortality can be seen [4], but it still remains unclear whether the majority of deaths occur early or late. In some reports, 70-80% of all deaths in acute pancreatitis are attributed to infected necrosis

[1, 5, 6], which means late mortality. On the contrary, other studies indicate that at least half of deaths occur early and are primarily related to MOF rather than to infection [7, 8, 9, 10, 11, 12].
The aim of the present study was to analyze the timing of death from severe acute pancreatitis in a large series of patients and to compare the clinical features of patients with early *vs.* late mortality.

PATIENTS AND METHODS

We retrospectively reviewed the medical charts and/or computerized medical records of all patients observed in the Centre for Pancreatic Disease of the Internal Medicine and Gastroenterology Departments of Cardarelli Hospital, Naples, Italy (one of the largest tertiary-care referral hospital in Italy) from October, 1984 to December, 2000. In this time-period, 1,150 episodes of acute pancreatitis occurring in 1,135 patients (431 males and 704 female, median age 61.5 years, range 18-93 years) were registered. The diagnosis of acute pancreatitis was based on the presence of appropriate clinical and radiographic evidence accompanied by increases (at least three times the upper the normal level) in serum amylase and/or lipase. The definition of 'severe' acute pancreatitis (SAP) was in accordance with the Atlanta classification [3]. The hospital records of all cases of acute pancreatitis were reviewed; as this article is focused on the general characteristics of the patients who died, the following data in this particular group were registered: demographic data, etiological factors, early prognostic signs (Ranson's and Glasgow criteria) [4] at 48 hours after admission, body mass index (BMI), presence or absence of necrosis, sterile *vs.* infected necrosis, early *vs*. late deaths, comorbidity, kind of treatment (conservative or surgical treatment), and year of admission. The cause of death was also investigated. Pancreatic necrosis was defined by characteristic abnormalities on dynamic contrast enhanced computerized tomography scan [1, 3] or during surgical procedures. Necrotic tissue was considered infected if percutaneous fine needle aspiration and a subsequent surgical specimen revealed organisms on tissue gram stain and/or culture.
Early deaths were defined as deaths occurring within 14 days after admission, whereas late deaths were defined as deaths which occurred more than 14 days after admission. Comorbidity was considered to be present if a pre-existing disease was an active problem before SAP became the principal disease; chronic obstructive pulmonary disease, cardiac insufficiency (New York Heart Association; NYHA class III or IV), renal insufficiency, liver cirrhosis, diabetes mellitus, malignant disease diagnosed within 3 years before the current episode, immunological disease or chronic immuno-suppressive medication) were taken into account.
The same group of physicians treated all the patients. The main protocol treatment variations throughout the period of the study were: a) endoscopic retrograde cholangio-pancreatography with sphincterotomy when indicated in biliary forms starting from 1989; b) routine antibiotic treatment (imipenem-cilastatin) in necrotizing forms starting from 1990; c) intravenous continuous antiproteases (gabexate mesilate) starting from 1993. Indications for surgery remained the same during the period considered in the present study; the principal indication was the occurrence of infection of necrosis, and, in a minority of cases, other typical surgical complications such as hemorrhage, pancreatic ascites, perforation, pseudocyst rupture or its rapid increase in size.

STATISTICS

The results of the continuous data were expressed as median with range. The comparison of the variables between the two groups (early *vs*. late mortality) was performed using the Mann-Whitney test, the Fisher's exact test, the chi-squared test, Mantel-Haenszel linear-by linear association,

and hierarchical log-linear models. Two-tailed P values less than 0.05 were considered statistically significant.

ETHICS

As the study was retrospective, no informed consent was requested and the protocol was not approved by an institutional review board.

RESULTS

During the study period (195 months), 1,150 episodes of acute pancreatitis were observed in our Centre; 408 (35.5%) episodes occurred in SAP patients (all of them were characterized by pancreatic necrosis) and 742 (64.5%) episodes occurred in mild forms (all with edematous pancreatitis). Most of these episodes occurred in patients suffering from biliary acute pancreatitis (790 cases, 68.7%); other etiologies were: alcoholic (75 cases, 6.5%), idiopathic (141 cases, 12.3%), biliary and alcoholic (52 cases, 4.5%), various (92 cases, 8%).

Ninety-two patients out of the 408 episodes with SAP (22.5%) underwent surgical treatment; the remainder (316 cases, 77.5%) were treated conservatively which means medical treatment plus endoscopic and/or percutaneous drainage procedures when indicated [13, 14]. None of the patients suffering from mild acute pancreatitis underwent pancreatic surgery.

Mortality

There were 55 deaths (4.8% of the whole series); 53 of these patients suffered from necrotizing pancreatitis and 2 patients had

Table 1. Characteristics of patients with early (less or equal to 14 days from admission) and late (more than 14 days from admission) deaths.

	Early deaths (n=28)	Late deaths (n=27)	P value
Age, years; median (range)	64.5 (34-93)	66.5 (30-84)	0.807[a]
Gender			0.790[b]
- Females	15 (53.6%)	13 (48.1%)	
- Males	13 (46.4%)	14 (51.9%)	
Etiology			0.943[c]
- Biliary	13 (46.4%)	12 (44.4%)	
- Idiopathic	8 (28.6%)	7 (25.9%)	
- Alcoholic	3 (10.7%)	4 (14.8%)	
- Post-ERCP	2 (7.1%)	1 (3.7%)	
- Other	2 (7.1%)	3 (11.1%)	
Ranson's score; median (range)	3.5 (1-9)	3.9 (1-8)	0.796[a]
Glasgow score; median (range)	4.4 (3-8)	4.8 (2-7)	0.813[a]
BMI, Kg/m^2; median (range)	22.5 (18-36)	23.6 (17-38)	0.726[a]
Comorbidity			0.851[d]
No comorbidity	6 (21.4%)	6 (22.2%)	
1-2 organ systems	11 (39.2%)	10 (37.0%)	
3-4 organ systems	9 (32.1%)	8 (29.6%)	
More than 4 organ systems	2 (7.1%)	3 (11.1%)	
Year of admission			0.736[d]
1984-1989	9 (32.1%)	8 (29.6%)	
1990-1994	10 (35.7%)	9 (33.3%)	
1995-2000	9 (32.1%)	10 (37.0%)	

ERCP: endoscopic retrograde cholangiopancreatography
BMI: body mass index
[a] Mann-Whitney U-test
[b] Fisher's exact test
[c] Chi-squared test
[d] Mantel-Haenszel liner-by-linear association

Table 2. Pathologic features in patients with early (less or equal to 14 days from admission) and late (more than 14 days from admission) mortality in acute pancreatitis.

	Early deaths (n=28)	Late deaths (n=27)	P value
Sterile necrosis	17 (60.7%)	5 (18.5%)	0.091
Infected necrosis	3 (10.7%)	20 (74.1%)	0.001
Necrosis without microbiological data	7 (25.0%)	1 (3.7%)	0.072
Edematous	1 (3.6%)	1 (3.7%)	0.785
		P<0.001	

Hierarchical log-linear model

edematous pancreatitis. All patients who died were experiencing their first episode of pancreatitis.

Early *vs*. Late Mortality

Early and late deaths were equally distributed (P=0.893): 28 patients (50.9%) died within 14 days from admission (median day of death 5.5, range 2-14 days) and 27 patients (49.1%) died later (median: 28 days, range 15-56 days). The two groups had no significant differences with respect to age, gender distribution, etiology, Ranson's and Glasgow scores, BMI, comorbidity and year of admission (Table 1). Twenty-seven (96.4%) of the 28 patients with early mortality had necrotizing pancreatitis *vs.* 26 (96.2%) of the 27 patients with late mortality (P=1.000). However, the pathological features between the early and the late mortality patients were significantly different (P<0.001). In particular, a significantly (P=0.001) higher number of people died from infected necrosis in the late death group (Table 2).
The causes of death are reported in Table 3. Early deaths resulted from multi-organ failure in 24 of the 28 (85.7%) patients. Late deaths occurred post-operatively in 20 patients with infected necrosis (16 presented also MOF), two of these also presented hemorrhagic complications (one intestinal and one intra-pseudocystic).
Only 3 patients (10.7%) were operated on in the early death group (two for infected necrosis and one for intestinal perforation) *vs*. 22 (81.5%) who underwent surgical treatment in the late death group (P<0.001).

DISCUSSION

Discrepancies exist in the literature regarding the patterns of mortality and morbidity in SAP [6, 8, 9, 10, 12, 15, 16, 17, 18, 19]; in fact, early mortality is reported in percentages ranging from 0 to more than 80% (mean value, 50.6%; Table 4). The reasons for such a wide range of early mortality rates in SAP

Table 3. Cause of death in patients with early (less or equal to 14 days from admission) and late (more than 14 days from admission) mortality.

	Early deaths (n=28)	Late deaths (n=27)
MOF	23	6
Infected necrosis + MOF	1	16
Infected necrosis	1	4
Myocardial infarction	1	-
Cardiac arrhythmias	1	1
Cerebral stroke	1	-

MOF: multi-organ system failure

Table 4. Reports in the literature on the incidence of early deaths in acute pancreatitis.

	Deaths from acute pancreatitis	
	Total number	Early deaths
Renner *et al.*, 1985 [8]	405	60.0%
Wilson *et al.*, 1988 [15]	126	55.5%
de Beaux *et al.*, 1995 [16]	17	52.9%
Lankisch *et al.*, 1996 [17]	37	56.7%
Talamini *et al.*, 1996 [9]	17	82.3%
Uhl *et al.*, 1999 [18]	32	21.0%
McKay *et al.*, 1999 [10]	?	53.7%
Mutinga *et al.*, 2000 [12]	17	47.0%
Gloor *et al.*, 2001 [6]	10	0%
Isenmann, 2001 [19]	36	55.5%
Present study	55	50.9%

are not easily understandable. Mutinga *et al*. [12] suggested some possible explanations: a) in various studies, the information comes primarily from surgical wards rather than from an entire hospital population; b) some patients who are severely ill during the first days of SAP may not be well enough to be transferred to hospitals which are specialized in pancreatic diseases; c) some late deaths may occur among patients who undergo early surgical debridement for sterile necrosis. The increased mortality rate observed in severe patients [19] is probably related to the fact that surgical intervention frequently converts sterile necrosis to infected necrosis; this finding was nearly 60% in our previous experience [13].

The present study shows that approximately half of the deaths occur within two weeks; mostly as a result of MOF. Early organ failure seems to be characterized by a high incidence of extended pancreatic necrosis, in particular, on the extent of an *intra*-pancreatic necrotic parenchyma [19]. An additional feature of MOF occurring in the early phase of SAP is linked to the extremely high risk of ongoing and progressive organ failure once early organ failure exists at admission [20]. Other recent data suggested that the progression of organ failure during the first week of hospitalization is associated with increased mortality [21, 22]. Some reports indicated that patients with SAP at high risk for developing severe systemic inflammatory response syndrome and MOF are not only those with infected necrosis but also elderly patients with comorbid medical problems [4, 6]. In the present study, etiology, age, and pre-existing diseases had no influence on the mortality timing and this confirms our previous experience published in 1998 [23]. In addition, early prognostic indicators such as Ranson's and Glasgow criteria did not differentiate patients at risk for early *vs.* late mortality from SAP. Similarly, BMI values were not significantly different in patients with early and those with late mortality, and the majority of these patients were not obese (Table 1). Some studies have reported that a high BMI represents a negative prognostic factor in SAP in that it is highly associated with an increased MOF incidence and early/late mortality [6, 24], but others [9, 12, 25] have not confirmed this relationship. The behavior of all the abovementioned features (listed in Table 1) seems to confirm our practical clinical perception that, once the pathogenetic mechanisms have initiated the disease, the course and outcome (including the occurrence of a fatal event in the early or late phase) of SAP are not influenced by underlying etiological factors, demographic/ physical features or comorbidity.

The results of the present study emphasize the relevant clinical importance of MOF occurrence in the outcome of SAP. Considering all the patients who died (55 cases), we found that MOF represented the cause of death in 83.6% (46 patients); in particular, 17 of the 22 (77.3%) patients with infected necrosis showed two or more organ system failure directly related to the fatal outcome (Table 3). since the treatment of infected pancreatic necrosis (i.e., antibiotics, surgical necrosectomy and drainage procedures) is nowadays standardized and widely accepted [1, 2, 3, 4, 26, 27, 28, 29] whereas management of MOF still remains unsatisfactory in SAP [4, 26, 28], the main therapeutic problem during the entire course of SAP is posed by the correct and continuous support and restoring of organ system failure. Very few data are available in the literature regarding the reports of patients with the so-called 'fulminant course' of SAP, who represent the paradigm of a deleterious and unstoppable MOF condition. In the series of McKay *et al*. [10], 40% of all deaths occurred within 3 days of hospital admission, despite the considerable progress which intensive care treatment has made during the past decades. In our opinion, the following questions should be asked when attempting to decrease MOF-related mortality in SAP: a) Should we perform more endoscopic sphincterotomies?; b) Is a different treatment strategy necessary in older patients?; c) Do the patients benefit from an earlier specific treatment, i.e. antiproteases, cytokines modulators and so on ?; d) Is more enteral

feeding necessary?; e) Do patients benefit from more aggressive intensive care modalities? In addition, a more in-depth knowledge of the pathologic mechanisms which link the infection of pancreatic necrosis with MOF, septic-like syndrome, and systemic inflammatory response syndrome [30] appears to be basic for a more efficacious treatment of patients having a high risk of late mortality.

In clinical practice, SAP still remains a serious medical problem; improvement in its mortality rate will require new strategies to counteract early MOF and to better treat the systemic complications associated with the glandular necrosis.

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Keywords Mortality; Multiple Organ Failure; Necrosis; Pancreatitis, Acute Necrotizing

Abbreviations NYHA: New York Heart Association; SAP: severe acute pancreatitis

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