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ORIGINAL ARTICLE

Proinflammatory Cytokines in Alcohol or Gallstone Induced Acute Pancreatitis. A Prospective Study

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ABSTRACT

Objectives If differences of inflammatory pathways in acute pancreatitis exist for various etiologies, selective and specific anti-inflammatory and other modulatory treatment regimens might be indicated. Circulating levels of prominent proinflammatory cytokines IL-6, 8, 18, and TNF-alpha were measured in patients having their first attack of either alcohol- or gallstone-induced acute pancreatitis. **Methods** Seventy-five consecutive patients were prospectively included over a 15-month period, sixty of them being either alcohol- or gallstone-induced. All patients were treated according to a standardized algorithm. Blood samples were obtained immediately on admission and, again, at days 1, 2, and 14. **Results** A significant effect of the etiology on the levels of IL-8 in the alcohol group as compared to the gallstone group (P=0.003) was found. No etiologic differences were observed for IL-6, IL-18, TNF-alpha, or CRP. Furthermore, no significant differences, either regarding the need for treatment at the intensive care unit or of 30-day mortality, were found. **Conclusion** The present study confirms previous findings and supports the hypothesis that, except for IL-8, the biochemical profile and clinical outcome is independent of the underlying etiology. Revealing the complex spatial and temporal profile of proinflammatory cytokine expression in acute pancreatitis is necessary and important for the development of a more targeted rational therapy.

INTRODUCTION

Acute pancreatitis is an inflammatory condition which can lead to severe extrapancreatic organ dysfunction and failure. Despite intensive research and improved supportive treatment, acute pancreatitis remains a serious and potentially lethal disease with an overall 30-day mortality rate of about 10% [1]. A specific treatment regimen for acute pancreatitis has not yet been identified.

The two prevailing etiologies of acute pancreatitis are alcohol and gallstones, which seem to act through different pathogenic mechanisms to induce pancreatic acinar cell damage and, subsequently, acute pancreatitis. Alcohol abuse is the most common cause of acute pancreatitis in men while gallstone migration into the common bile duct constitutes the leading etiology in women [2]. Alcohol is partially metabolized in the pancreas and may cause reduced blood flow and the generation of free oxygen radicals [3], thereby increasing the risk of developing acute pancreatic inflammation. Gallstones, on the other hand, are believed to act through obstruction of the ampulla of Vater, thereby causing retention and stasis of pancreatic secretory fluids and the reflux of bile into the pancreatic duct [4, 5]. Although the pathogenic mechanisms of the induction of acute pancreatitis may be different, patients with acute pancreatitis are treated identically without the attempt to target any differences. This is in accordance with the current general opinion which is that, once acute pancreatitis is initiated, the ongoing inflammatory response and outcome is independent of the underlying mechanism of induction. Thus, previous studies have not found any significant difference in mortality or need for admittance to an intensive care unit among the different etiologies of acute pancreatitis [6, 7, 8].

Cytokines play a pivotal role in the pathogenesis of acute pancreatitis by driving the subsequent

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Abbreviations ASAT: aspartate aminotransferase; CRP: C-reactive protein; CT: computerized tomography; ERCP: endoscopic retrograde cholangiopancreatography; IL: interleukin; MRI: magnetic resonance imaging; TNF-alpha: tumour necrosis factor alpha; US: ultrasound

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inflammatory response which leads to tissue damage and organ dysfunction, or failure in more severe cases. Thus, an inflammatory response of a yet unknown origin in acute pancreatitis may lead to the release of reactive oxygen species which might also have a potential for inducing the autodigestion of acinar cells [9]. This step induces pancreatic necrosis which triggers both recruitment and activation of inflammatory cells [9, 10].

Local recruitment and activation of inflammatory cells in acute pancreatitis may lead to the production of proinflammatory cytokines, such as interleukin (IL) 6, 8, 18 and tumour necrosis factor alpha (TNF-alpha) [11, 12, 13, 14, 15]. Furthermore, such proinflammatory cytokines may subsequently activate pancreatic stellate cells and trigger both fibrin deposition and scarring [16, 17] in a similar fashion to the outcome of alcoholic hepatitis leading to liver fibrosis and cirrhosis. However, little is known about circulating concentrations of these and other inflammatory cytokines in relation to etiology [18]. If differences in the inflammatory pathways exist for various etiologies, such an observation could prompt a more rational therapeutic approach with selective and specific anti-inflammatory and other modulatory treatment regimens.

We hypothesized that the plasma profile of circulating inflammatory mediators differs with regard to etiology and, thus, the purpose of the present study was to describe circulating levels of a selection of four prominent proinflammatory cytokines in patients having their first attack of either alcohol- or gallstone induced acute pancreatitis.

MATERIAL AND METHODS

Patients

During a 15-month period (2004-2005), 75 patients having their first attack of acute pancreatitis were admitted to a regional pancreatic centre and prospectively included in the study. Only patients with alcohol- or gallstone-induced acute pancreatitis were included. All patients were treated according to a standardized algorithm, based on the United Kingdom guidelines of 1998 [19]. A case record form was registered for each patient, including age, gender, smoking and drinking habits, daily use of prescribed medicine, previous hospitalizations/admittances and possible abdominal operations.

Acute pancreatitis was defined as the acute onset of upper abdominal pain, combined with an elevated plasma amylase level of more than 3 times the upper normal level, with no other obvious explanations.

Alcohol-induced acute pancreatitis was defined as a daily consumption exceeding 30 g of alcohol for men, 20 g for women, or 50 g/day of alcohol one month prior to hospitalization, according to the guidelines for alcohol consumption issued by the Danish Medical Health Authorities [20], accompanied by the exclusion of gallstones by at least 2 of the following examinations: ultrasound (US), contrast-enhanced computerized tomography (CT) scan or magnetic resonance imaging (MRI). Patients with pancreatic calcifications, cysts or other signs of chronic pancreatitis were excluded from the study. Gallstone-induced acute pancreatitis was defined as a plasma level of aspartate aminotransferase (ASAT) greater than 150 U/L in combination with the presence of gallstones or sludge identified at US, MRI, or endoscopic retrograde cholangiopancreatography (ERCP).In addition, medical records were carefully investigated for other possible causes of acute pancreatitis, including hypertriglyceridemia, hypercalcemia, post-ERCP- or drug-induced acute pancreatitis. Patients with a history of alcohol use and in whom gallstones were detected on diagnostic imaging were excluded. Severe acute pancreatitis was defined as a plasma C-reactive protein (CRP) value above 210 mg/L within the first 72 hours after admission and/or a Glasgow Score of more than 3 [19, 20]. All patients meeting these criteria underwent a CT scan of the pancreatic region.

To assess the potential relationship between etiology and the development of organ complications, the criteria as defined by Uhl *et al*. [18] were applied.

ELISA Technique

Venous blood samples were taken immediately upon admission (day 0) and, again, on days 1, 2, and 14 after admission. Blood was drawn from an antecubital vein in 7 mL EDTA tubes (15% 0.084 mL) and gently mixed. Following this procedure, the plasma was isolated and stored at -80° C until subsequent analysis.

Measurements of IL-6, IL-8, IL-18 and TNF-alpha

Sandwich ELISA techniques for human IL-6, IL-8 and TNF-alpha (Amersham Pharmacia Biotech, Buckinghamshire, England) and human IL-18 (Medical & Biological Laboratories Co, Nagoya, Japan) were applied. Briefly, 100 µL non-diluted (IL-6, TNF-alpha); 50 µL 1:2 diluted (IL-8); 50 µL 1:5 diluted (IL-18) were preincubated with a specific monoclonal antibody, followed by the addition of polyclonal antibodies, which were either biotinylated (IL-6, IL-8, TNF-alpha) or conjugated with horseradish peroxidase (IL-18). Washing and aspiration removed unbound antibodies, and a colorimeric reaction proportional to the plasma concentration of the cytokines was performed with a substrate specific for the enzyme (tetramethylbenzidine (TMB) or TMB/H_2O_2 (IL-18 only)). Light absorbance was assessed by an automatic ELISA reader (Multiskan Ascent Reader, Thermo Labsystems, Cheshire, United Kingdom) at 450 nm with a correction wavelength of 620 nm for IL-18 only. The detection limits were 0.63 pg/mL, 25 pg/mL, 36 pg/mL, and 0.31 pg/mL for IL-6, IL-8, IL-18 and TNF-alpha, respectively, and the coefficient of variation was less than 0.10 in all analyses. All samples were run in duplicate.

ETHICS

The study was carried out according to the Helsinki V Declaration. The Scientific Ethics Committee of Copenhagen and Frederiksberg approved the study, and all patients gave their written consent prior to inclusion in the study (approval number: KF 01-143/03).

STATISTICS

Descriptive statistics are given by means of median (minimum-maximum) and frequencies (absolute and relative).

The association between baseline characteristics (gender: male/female; severity: mild/severe; need of the intensive care unit: yes/no; necrosis on CT-scan: yes/no; 30-day mortality: yes/no), and etiology (alcohol/gallstone) was evaluated using the Fisher's exact test. Differences in age between alcohol and gallstone-induced pancreatitis were evaluated using one-way analysis of variance (ANOVA). The association between complications (renal insufficiency: yes/no; intestinal obstruction: yes/no; jaundice: yes/no; cardiovascular insufficiency; yes/no; and pulmonary insufficiency: yes/no) in patients and etiology (alcohol/gallstone) was evaluated using the Fisher's exact test.

Differences in IL-6, IL-8 and IL-18, TNF-alpha and CRP between etiologies (alcohol/gallstone) and severity (mild/severe) over time (0, 1, 2, 14 days) were evaluated by repeated measurements (ANOVA). Main effects and interactions were initially included in the analysis. Backward elimination was used to obtain the resulting model. The autocorrelation between repeated measurements for the same patient was taken into account using an autoregressive correlation structure adjusted by the number of days between two consecutive measurements. The assumptions for using an analysis of variance were evaluated using the Shapiro-Wilks' test for normality and visual inspection of residual plots to evaluate equal variances. Due to skewed distributions, a rank-transformation of IL-6, IL-8, IL-18, TNF-alpha and CRP was used prior to analysis.

A 5% significance level was applied. The analyses were performed using the Statistical Analysis System (SAS, version 9.1.3).

RESULTS

Demographic Data

Seventy-five patients were included in the study. The etiology was uncertain, idiopathic, mixed or of other origin in 15 of the 75 patients (20.0%). However, a single etiology existed for 60 patients, of which 22 (36.7%) were alcohol-induced, and the remaining 38 (63.3%) were gallstone-induced (Table 1). The overall median age was 60 years (range 19-94 years); patients in the gallstone group were significantly older than those in alcohol group (Table 1). Females dominated over males in the gallstone-induced acute pancreatitis group while there were more males in the alcohol-induced acute pancreatitis-group (Table 1). Twenty-five patients (41.7%) were admitted within 24 hours from the onset of pain, 11 (18.3%) within 24 to 48 hours, and 24 (40.0%) after more than 48 hours, with no significant difference in relation to etiology (P=0.124). No significant differences in levels of IL-6, IL-8, IL-18, TNF-alpha, and CRP were found between early (less than 48 hours from onset of pain) and late (more than 48 hours) admission (data not shown). Additionally, we performed statistical comparisons of putative differences in time related to etiology, and no difference in time from symptom debut to hospital admission in relation to the different etiology was detected (IL-6: P=0.702; IL-8: P=0.512; IL-18: P=0.718; TNF-alpha: P=0.401; CRP: P=0.381). None of the patients were treated with any type of open surgical procedure.

Severity of Disease

A total of 23 (38.3%) patients developed severe acute pancreatitis with no significant difference among etiologies (P=1.000). There were no significant differences regarding the need for treatment in the intensive care unit or of 30-day mortality (Table 1).

Pulmonary insufficiency was the most frequent complication, occurring in 18.3% of patients, again with no differences concerning etiology (P=0.731). Finally, no etiology-related significant differences were observed in the development of multi-organ failure (Table 2).

Table 1. Base-line characteristics of 60 patients having their first attack of acute pancreatitis, stratified by etiology. P values are given for the association between the baseline characteristics and etiology.

	Alcohol (no.=22)	Gallstone (no.=38)	P value
Gender:			0.001 [a]
- Males	16 (72.7%)	10 (26.3%)	
- Females	6 (27.3%)	28 (73.7%)	
Severe acute pancreatitis:	8 (36.4%)	15 (39.5)	1.000 [a]
- Defined by CRP	8	15	
- Defined by Glasgow criteria	4	8	
Need of intensive care unit	1 (4.5%)	2 (5.3%)	1.000 [a]
Necrosis on CT-scan	0	4 (10.5%)	0.286 [a]
30-day mortality	2 (9.1%)	2 (5.3%)	0.619 [a]
Age: median (range); years	52 (19-71)	66 (23-94)	0.003 [b]

[a] Fisher's exact test
[b] One-way ANOVA

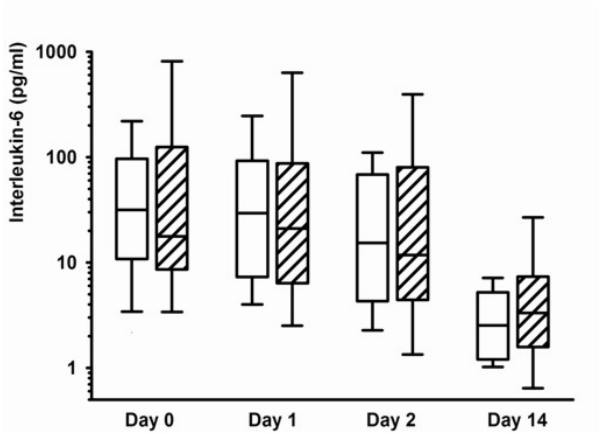

Figure 1. Box-plot of plasma IL-6 concentrations in relation to etiology in patients having their first attack of alcohol- or gallstone-induced acute pancreatitis. Boxes indicate the range between the 25th and 75th percentiles of the data. The horizontal line represents the medians. Bars indicate the 95%-interpercentile range. Open boxes represent alcohol induced acute pancreatitis and dashed boxes gallstone induced acute pancreatitis.

Interleukins

IL-6

A significant difference in severity over time (a significant interaction, P=0.007) was found for IL-6. During the first 24 hours, IL-6 peaked for severe acute pancreatitis and returned to a significantly lower level at day 14. There were, however, no differences between groups of etiology (P=0.448) (Figure 1).

IL-8

There was a significant effect of etiology over time (a significant interaction, P=0.027), although no significant differences in IL-8 were found between the etiology groups on days 0, 1, 2, and 14 (Figure 2).
A significant effect of severity over time (P<0.001) and of etiology over severity (P=0.014) was found. For patients with gallstone-induced acute pancreatitis, patients with mild acute pancreatitis had significantly lower levels of IL-8 (P<0.001) as compared to patients with severe acute pancreatitis. For patients with mild acute pancreatitis, patients with an alcohol-induced acute pancreatitis had significantly (P=0.021) higher levels of IL-8 as compared to patients with gallstone-induced acute pancreatitis (Table 3).

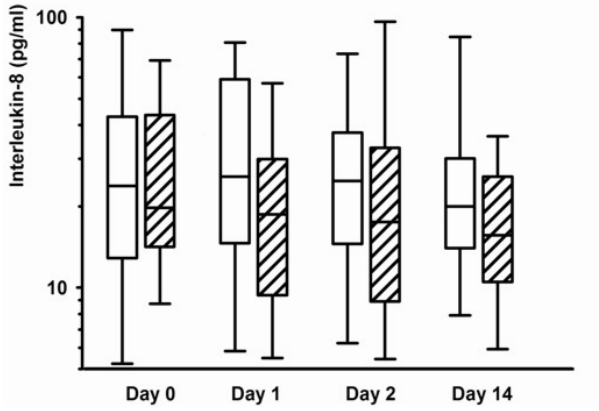

Figure 2. Time course of plasma IL-8 concentrations in relation to etiology in patients having their first episode of acute pancreatitis. Boxes indicate the range between the 25th and 75th percentiles of the data. The horizontal line represents the medians. Bars indicate 95%-interpercentile range. Open boxes represent alcohol-induced acute pancreatitis and dashed boxes gallstone-induced acute pancreatitis.

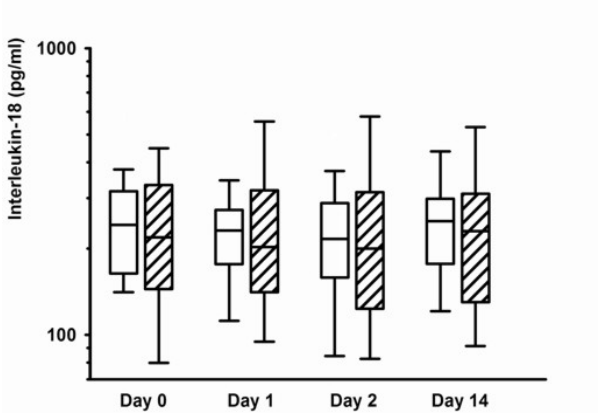

Figure 3. Box-plot showing plasma profile of IL-18 in relation to etiology in patients having their first episode of acute pancreatitis. Boxes indicate the range between the 25th and 75th percentiles of the data. The horizontal line represents the medians. Bars indicate the 95%-interpercentile range. Open boxes represent alcohol-induced acute pancreatitis and dashed boxes gallstone-induced acute pancreatitis.

Table 2. Complications in 60 patients having their first attack of acute pancreatitis, stratified by etiology.

	Alcohol (no.=22)	Gallstone (no.=38)	*P value* [a]
Renal insufficiency	2 (9.1%)	4 (10.5%)	1.000
Intestinal obstruction	0	3 (7.9%)	0.292
Jaundice	6 (27.3%)	19 (50.0%)	0.108
Cardiovascular insufficiency	1 (4.5%)	2 (5.3%)	1.000
Pulmonary insufficiency	3 (13.6%)	8 (21.1%)	0.731
Multi-organ failure	2 (9.1%)	9 (23.7%)	0.299

[a] Fisher's exact test

IL-18

Levels of IL-18 did not differ significantly over time (P=0.172) or in relation to etiology (P=0.625) (Figure 3). Significantly lower levels of IL-18 were seen in mild acute pancreatitis as compared to severe acute pancreatitis (P=0.016). No difference between the alcohol and the gallstone groups was found in severe acute pancreatitis (P=0.822).

TNF-alpha

Plasma levels of TNF-alpha did not change significantly over time (P=0.615) in relation to etiology (P=0.143) or in relation to severity (P=0.196) (Figure 4).

Table 3. IL-8 levels (pg/mL) in relation to the etiology and severity of acute pancreatitis. Results are shown as the median (range).

	Mild acute pancreatitis		Severe acute pancreatitis	
	Alcohol (no.=14)	Gallstone (no.=23)	Alcohol (no.=8)	Gallstone (no.=15)
Day 0	25 (5-153)	16 (0-79)	15 (4-46)	29 (9-2,264)
Day 1	26 (5-132)	13 (3-48)	26 (5-83)	29 (13-860)
Day 2	26 (6-142)	13 (1-110)	19 (5-81)	26 (10-613)
Day 14	20 (7-211)	14 (0-71)	24 (8-85)	27 (7-101)

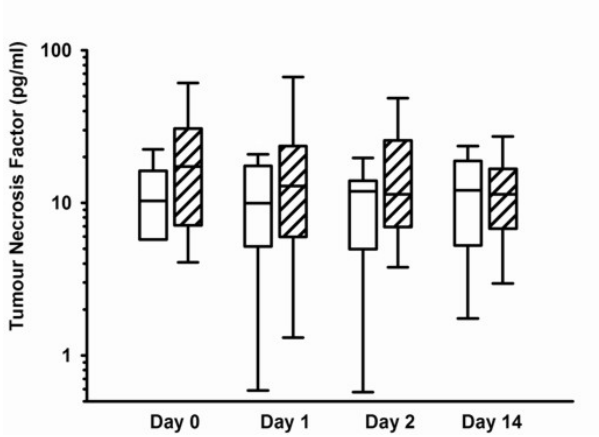

Figure 4. Plasma profile of TNF-alpha in patients having their first episode of alcohol- and gallstone-induced acute pancreatitis. Boxes indicate the range between the 25th and 75th percentiles of the data. The horizontal line represents the medians. Bars indicate the 95%-interpercentile range. Open boxes represent alcohol-induced acute pancreatitis and dashed boxes gallstone-induced acute pancreatitis.

CRP

There was no significant difference in CRP between alcohol- and gallstone-induced acute pancreatitis (P=0.951); however, a significant effect of severity over time (a significant interaction, P<0.001) was revealed. CRP values changed over time for mild and severe acute pancreatitis, with significantly higher values on days 1 and 2 as compared to days 0 and 14. CRP was significantly higher on day 0 as compared to day 14 (Figure 5).

DISCUSSION

Alcohol and gallstones may induce pancreatic inflammation through different pathogenic pathways, but with a similar clinical outcome [3, 4]. Whether such differences might be reflected in the biochemical profile of some specific proinflammatory mediators in the circulation was investigated in the present study.

Previous investigations on this topic were limited by a lack of consensus on the appropriate definitions of the diagnosis of acute pancreatitis or in classifying the severity of disease. Furthermore, in most studies, the group of alcohol-induced acute pancreatitis included acute attacks among patients with chronic pancreatitis in which the mortality rates are rather low, making comparisons of morbidity and mortality rates almost impossible. Another difficulty in interpreting the results of previous studies is the lack of a standardized treatment algorithm. In contrast, we only included patients having an apparent first attack of acute pancreatitis, and all patients were diagnosed and treated according to international guidelines [19]. Additionally, we applied precise definitions of alcohol- and gallstone-induced acute pancreatitis, and patients with other etiologies of acute pancreatitis were excluded.

There is, however, no consensus on the definite criteria for alcohol-induced acute pancreatitis. Our definition of alcohol-induced acute pancreatitis, based on the recommendations for maximal daily alcohol intake issued by the Danish Medical Health Authorities [20], may be debatable since 30 g of alcohol on a daily basis for men and 20 g for women for a minimum of one month prior to hospitalization may actually be a rather low threshold. On the other hand, a clear dose-response relationship between alcohol and the induction of acute pancreatitis has not been established.

In a large multicenter study, Gullo *et al*. [6] did not find any significant differences in mortality rates among the different etiologies of acute pancreatitis. Another retrospective study supported this observation [21]. In a prospective study consisting of 51 patients, Nordestgaard *et al*. [22] found no differences in mean serum amylase levels among different etiologies. Lankisch *et al*. [7] retrospectively evaluated a relationship between etiology and course of the disease, and found no significant etiologic differences between the groups as regards the need for artificial ventilation, creatinine blood levels, duration of hospital stay or mortality rate. Recently, a retrospective study from our group, applying same inclusion criteria as the present study, showed no differences in morbidity or mortality between the alcohol and gallstone groups of acute pancreatitis [8]. Thus, the results of the present study are consistent with these findings and support the current opinion that acute pancreatitis should be treated with supportive measures and with expectancy.

Currently, a number of clinical and experimental studies suggest that interleukins may play a key role in the pathogenesis of local and systemic complications of acute pancreatitis. Previous studies have observed an early increase in IL-6, which regulates the acute-phase response, such as CRP produced by hepatocytes, and a significant difference in plasma levels between mild and severe acute pancreatitis has been found [11, 23, 24]. The present results thus confirm these findings.

A significant effect of etiology on IL-8 plasma values was found here, which is in accordance with a recent population-based survey demonstrating that the proportion of individuals with elevated circulating IL-8 levels (i.e., greater than 10 pg/mL) increase with the level of alcohol consumption [25]. IL-8 is primarily

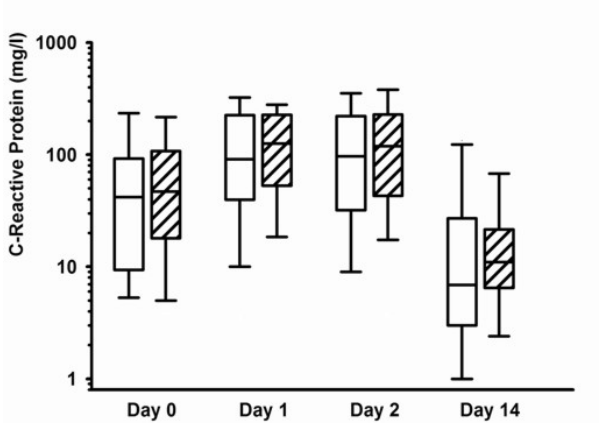

Figure 5. Box-plot showing plasma CRP concentrations in relation to etiology in patients having their first attack of acute pancreatitis. Boxes indicate the range between the 25th and 75th percentiles of the data. The horizontal line represents the medians. Bars indicate the 95%-interpercentile range. Open boxes represent alcohol-induced acute pancreatitis and dashed boxes gallstone-induced acute pancreatitis.

synthesized and released by macrophages and endothelial cells, exerting a chemotactic effect on neutrophils and stimulating their release [26]. However, IL-8 is able to activate a wide range of signaling molecules in cells other than neutrophils [27], including hepatocytes, which could explain the higher values found in the alcohol group. Thus, IL-8 has also been found to correlate with markers of acute liver damage [28, 29, 30]. As defined by our criteria for organ insufficiency, only two patients with alcohol-induced acute pancreatitis presented with signs of organ failure on admission. None of these patients showed any significant increase in IL-8 values.

No significant differences in IL-18 plasma levels between the alcohol- and gallstone-induced acute pancreatitis groups were detected. Ueda *et al*. [13] investigated values of IL-18 between different etiologies of acute pancreatitis on admission, without finding any significant difference.

The TNF-alpha values in the present study did not differ over time between mild and severe cases, or in relation to etiology. A number of previous studies have described several limitations in the detection of TNF-alpha concentrations in the circulation, such as short half-lives, paracrine activities and a counterbalance by circulating inhibitors [11, 12].

A prospective study by Uhl *et al*. [18] analyzed the etiological groups of acute pancreatitis with respect to differences in the severity, related complications and mortality rates, with no significant variations. Furthermore, the course of serum enzymes (lipase, ASAT) and surrogate markers of necrosis (CRP, $alfa_1$-antitrypsin, $alfa_2$-macroglobulin and lactate dehydrogenase) was investigated, revealing that, within 24 hours, significantly higher levels of ASAT were detected in gallstone acute pancreatitis as compared to the other etiologic groups [18]. In the present study, plasma CRP values differed significantly over time, as expected, but they were not influenced by etiology, which again is not surprising, as it takes 48-72 hours before CRP is fully induced by the liver. Furthermore, since IL-6 is a major challenger and regulator of CRP synthesis in the liver, it was expected that the CRP profile would be independent of etiology, as was the case for IL-6.

CONCLUSIONS

The present study supports the hypothesis that the biochemical profile and clinical outcome is independent of an underlying etiology, once acinar cell damage and eventually acute pancreatitis is induced. Thus, both circulating IL-6 and IL-8 seem to be pivotal mediators in the pathogenesis of acute pancreatitis. Further studies focusing on these two cytokines and other mediators are needed to elucidate their more specific role in acute pancreatitis. Revealing the complex spatial and temporal profile of proinflammatory cytokine expression is necessary and important for the rational development of a more targeted therapy for acute pancreatitis in the future.

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Conflict of interest The authors have no potential conflicts of interest

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