Systemic Lupus Erythematosus as a Cause and Prognostic Factor of Acute Pancreatitis

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ABSTRACT. ***Objective.*** To perform a systematic analysis and case-control study of our patients with systemic lupus erythematosus (SLE) to determine the prevalence of acute pancreatitis (AP).

Methods. All episodes of AP in SLE patients were identified (July 1984–July 2001). Prevalence was calculated. Etiology for each AP event was classified into mechanical, toxic-metabolic, or idiopathic. AP severity was defined based on Atlanta criteria. SLE disease activity was scored using Mex-SLEDAI index. A control group of non-SLE patients with AP was designed to establish the risk of developing severe or fatal idiopathic AP in patients with SLE.

Results. Forty-nine AP episodes were identified in 35 SLE patients (30 ± 14 yrs old, 94% female). Prevalence was 3.5%. A single episode was present in 26 patients. Identified AP causes were mechanical in 14 and toxic-metabolic in 10. Seventeen episodes were considered idiopathic. At least one drug related to AP was administered in 13 episodes. Corticosteroids were in use in 32 episodes, and as the only drug in 16. Mex-SLEDAI scores were significantly higher in idiopathic events. In the case-control analysis, idiopathic AP was more frequent in SLE cases (46% vs 14%). The strength of association of AP severity and related mortality was higher in SLE patients (OR 8.6 and 7.5, respectively).

Conclusion. AP is not a highly prevalent manifestation of SLE. Idiopathic cases predominate and show increased SLE activity. Drug consumption does not seem to participate in AP development. SLE episodes are more severe and frequently fatal. (J Rheumatol 2004;31:707–12)

Key Indexing Terms:
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A case of acute pancreatitis (AP) complicating systemic lupus erythematosus (SLE) was described in 1939 by Reifenstein, *et al*[1]. Additional cases[2-13] and small series of patients[14-21] have since been reported supporting an association between both entities. However, in other authors' series[22,23] comprising 350 SLE patients, there were no instances of AP, and prevalence of the coexistence of these diseases has remained confusing.

Most articles have focused on the cause of AP in SLE as a result of pancreatic involvement by the disease, either through vascular damage[24-28] or, indirectly, by the use of drugs or the presence of another underlying disease[2,5,17-19]. Also, although common causes of AP[29,30] such as biliary disease, alcohol abuse, or hypertriglyceridemia can occur in SLE patients, they have not been considered in some reports[4,6,15,16,21].

The pathogenic mechanism responsible for pancreatic damage in SLE awaits definition[31], but vascular damage as a cause has been stressed. This has included necrotizing vasculitis syndrome[24], occlusion of arteries or arterioles by thrombi resulting from either severe hypotension or antiphospholipid syndrome[26,27], and immune complex deposition with complement activation in the wall of pancreatic arteries[32].

Pancreatitis occurring in a patient with SLE can be fatal, but data regarding its actual severity and mortality have been equivocal[14,15,17,19], mostly because previous reports have lacked adequate patient selection and definition of criteria of AP severity. Thus, the low frequency of the association, and the bias resulting from a tendency to report selected cases, have all resulted in a lack of knowledge regarding prevalence, etiology, and outcome of AP in SLE. To learn about these we identified all SLE patients who had presented at least one event of AP. We defined its cause by analyzing the possible relationship with SLE activity and/or drug use. We determined the severity of AP according to the Atlanta criteria[33] and analyzed the resulting mortality. Finally, we designed a case-control study to investigate differences in the etiology and outcome of AP and to define SLE as a risk factor for severity and/or mortality.

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MATERIALS AND METHODS

Episodes of AP in SLE patients were identified in the institutional databases of SLE and AP; they included all hospital admissions of SLE patients as well as all episodes of AP studied between July 1984 and July 2001. In each case, an extensive review of the medical record was done. All patients had at least 4 American College of Rheumatology criteria (ACR 1982) for the classification of SLE. The diagnosis of AP was established by the presence of typical clinical symptoms with more than a 3-fold increase of serum amylase or lipase and/or morphological confirmation by computer tomography (CT) scan/ultrasonography or laparotomy. Cases diagnosed as AP at autopsy that had not been suspected clinically were excluded.

To calculate prevalence we had to limit the study period from January 1992 to July 2001, estimating it by the number of patients having at least one episode of AP within this period, divided by the total number of SLE patients who attended our institute in the same period[34].

We documented the age, sex, disease duration, and clinical manifestations of SLE prior to the first episode of AP diagnosed and treated at our institution. We classified the latter as early or late manifestation, occurring within or after the first 2 years of the disease, respectively, as determined by the first clinical manifestation attributable to SLE. Etiology of each AP episode was classified as mechanical, toxic-metabolic, or idiopathic[30]. Mechanical episodes included biliary (ultrasonographic evidence of gallstones, choledocholithiasis, or bile duct dilatation and/or serum liver chemistry compatible with obstructive jaundice, with no other obvious cause of the attack), obstructive [identified by CT scan and/or endoscopic retrograde cholangiopancreatography (ERCP)], and post-ERCP etiologies. Toxic-metabolic related episodes included a history of alcohol consumption (> 80 g/day), hypertriglyceridemia (≥ 500 mg/dl), and hypercalcemia[30], as well as patients with uremia in endstage renal disease (ESRD), irrespective of other concomitant metabolic abnormalities[18,35,36]. Cases were considered idiopathic if no cause could be identified. We noted drugs that related to AP development as those that had been administered during the month previous to the onset of each AP episode[30,37]. Special consideration was given to possible rechallenge. The mean daily steroid dose during the month previous to the episode of AP was also calculated. The Mexican version of the SLE Disease Activity Index (Mex-SLEDAI) was used to evaluate SLE activity during the episode of AP[38].

Complications of AP were classified as local (necrosis, infected necrosis, pseudocyst, and abscess) or systemic (renal, respiratory, cardiac and multiorgan failures, sepsis, gastrointestinal bleeding, and coagulopathy) according to the Atlanta criteria[33]. Severity was defined as the presence of any local or systemic complication. Mortality and cause of death during the AP episode were documented. In patients who survived, the mean followup after the first AP episode was calculated and clinical status at the last consultation was recorded.

A case-control study was designed to establish the risk of developing severe or fatal idiopathic AP in SLE. Cases included only SLE patients seen at our institution from the onset of their first AP episode. The control group consisted of non-SLE patients with AP. The group was selected from our databases, matched by frequencies by sex and number of AP episodes. The control-case ratio was 4:1.

Statistical analysis. Fisher's exact test was used for comparing categorical variables between cases and controls. SLE activity (according to Mex-SLEDAI) and other continuous variables were compared among groups using Mann-Whitney U test. To estimate the case probability, we calculated the odds ratio (OR) with 95% confidence intervals (95% CI) and the chi-square statistic test significance. A 2-tailed p value < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS/PC 10.0 for windows (SPSS, Chicago, IL, USA).

RESULTS

Forty-nine episodes of AP were identified in 35 patients. Data regarding AP onset were available for 41 events (32 patients). Twenty-six patients had a single episode of AP, while recurrent episodes occurred in 9 patients (2 in 6 patients, 3 in one, and 4 in 2).

Thirty-three patients were female (94%). Mean ages (± SD) at first manifestation and at diagnosis of SLE were 24 ± 10 and 26 ± 11 years, respectively. The mean age (± SD) at first AP episode was 30 ± 14 years. AP occurred in 14 patients within 2 years of the first clinical manifestation attributable to SLE and in 21 during the first 2 years after diagnosis.

Prevalence. Eight hundred ninety-five SLE patients were identified in the period studied for prevalence. Thirty-one had AP attacks, with a resulting prevalence of 3.5%.

Clinical manifestations of SLE. The most frequent early and late clinical manifestations of SLE were articular in 86% and 73%, mucocutaneous in 83% and 83%, general in 77% and 78%, hematological in 54% and 68%, and renal in 43% and 64%, respectively. Twenty percent of SLE patients had secondary antiphospholipid syndrome.

Etiology of AP. Etiological factors for AP were analyzed in the 41 events seen at our institution from their onset. Abdominal ultrasonography was performed in 83% of AP episodes, CT scan in 49%, ERCP in 22%, and endoscopic ultrasound in 10%. An apparent cause of AP was found in 24 episodes, whereas 17 events were considered idiopathic. Causes identified as mechanical (n = 14) were the following: choledocholithiasis (n = 10), obstructive (n = 3), and post-ERCP (n = 1). Obstructive cases consisted of one recurrent AP secondary to a pseudocyst that developed after an idiopathic episode (diagnosed by CT scan and at surgery), and 2 recurrent attacks caused by stenosis of Oddi's sphincter that resolved after sphincterotomy (both identified by ERCP). Toxic-metabolic etiologies (n = 10) included the following: hypertriglyceridemia (n = 3), ESRD (n = 5, one with hypertriglyceridemia, and another with hypercalcemia), and alcoholic (n = 2). Of the 5 episodes related to ESRD, 3 were associated with hemodialysis and 2 with peritoneal dialysis. No clinical evidence of thrombotic events was found in any case at AP onset. Of the 7 patients with SLE and secondary antiphospholipid syndrome, 5 had a biliary etiology, one was toxic-metabolic, and the remaining patients belonged to the idiopathic group.

Drug consumption. At least one drug implicated in the induction of AP (azathioprine, furosemide, isoniazid, metronidazole, and sulindac) had been administered prior to the onset of AP in 13 instances. There was no difference in exposure to these drugs among the various etiological groups. Seven patients were reexposed to these drugs because of precise medical indications, but in no instance did this rechallenge result in recurrence of AP (Table 1).

Corticosteroids were being consumed at the time of AP in 32 episodes, although their administration occurred in 20, in the absence of concurrent use of any of the other drugs previously noted. Of these, corticosteroids were the only

Table 1. Intake of drugs strongly related to AP development at AP onset according to etiology (I: mechanical; II: toxic-metabolic; III: idiopathic).

Etiological Group	Drugs		Rechallenge*	Prednisone ± Other Drugs		Prednisone Only	
Episodes, n	Episodes, n	Drugs, n	Drugs, n	Episodes, n	Mean Dose ± SD	Episodes, n	Mean Dose ± SD
I (n = 14)	4	4	1	12	19 ± 16	8	24 ± 18
II (n = 10)	3	5	3	7	26 ± 19	5	10 ± 4
III (n = 17)**	6	7	4	13	21 ± 16	7	15 ± 14

* Negative rechallenges. There were no positive drug rechallenges. ** One patient from group I and one patient from group III died.

drug in 16, were associated with danazol in 2, and with thalidomide in the other 2. There was no difference in the frequency of corticosteroid administration or in the dosing among etiological groups (Table 1).

Immunosuppressive treatment at onset of idiopathic episodes of AP was as follows: 4 patients were without immunosuppressive treatment, 10 were receiving corticosteroids alone, and 3 patients were receiving both corticosteroids and azathioprine. In all cases corticosteroids were either increased (n = 13) or started (n = 4) at doses ≥ 1 mg/kg/day of prednisone. Four received methylprednisolone boluses followed by ≥ 1 mg/kg/day of prednisone. Azathioprine was discontinued in the 3 patients who received it prior to the AP attack.

SLE disease activity. Mex-SLEDAI scores disclosed significantly higher lupus activity at the time of the idiopathic episodes of AP compared to all other episodes of AP (p = 0.009) or to the group with mechanically related episodes (p = 0.012) (Table 2). When idiopathic AP episodes with no or < 1 week of immunosuppressive treatment at AP onset (n = 7) were compared to those using corticosteroids and/or azathioprine (n = 10), no significant differences on Mex-SLEDAI scores were found (median 11 vs 8, respectively).

Severity, mortality, and followup. Twenty-three of the 41 (56%) episodes of AP were severe irrespective of their cause (mechanical: 6/14, toxic-metabolic: 6/10, idiopathic: 11/17). When analyzing only the 32 first episodes seen at our institution, we found that 22 (69%) had been severe (3 recurrent episodes, with 2 being severe) regardless of etiological group (mechanical: 6/10, toxic-metabolic: 5/7, idiopathic: 11/15). Seven patients (20%) died during an AP episode (6 in their first episode, and one in her second). Death was related to multiple organ failure and/or sepsis in 5 patients, to pulmonary edema developed at the time of the episode of AP as a complication of ESRD in one, and to pulmonary hemorrhage in the remaining patient. In these 7 patients the cause of the AP was mechanical in 4, toxic-metabolic in one, and idiopathic in 2.

Outcome of idiopathic cases was not significantly different when episodes of patients without previous immunosuppressive treatment (4 severe out of 4) were compared to those using corticosteroids (4 severe out of 10) or corticosteroids and azathioprine (3 severe out of 3). Two patients died, one from multiorgan failure (no immunotherapy) and the other from acute respiratory distress syndrome (on corticosteroids and azathioprine).

Patients who survived their first episode have been followed for a mean (± SD) 34 ± 32 months. Six patients developed a total of 9 episodes during this period and 4 died of causes unrelated to AP.

Case-control analysis. Thirty-two SLE patients were included in the case-control analysis. Idiopathic AP was more frequent in SLE cases (46%), while mechanical etiology was more frequent in controls (74%). In addition, the strength of association of AP severity and related mortality was higher in SLE cases than in controls (Table 3).

Table 2. Etiology of AP and activity index of SLE in each group.

Etiology of AP	n	Mex-SLEDAI Median (range)
Mechanical	14	3 (0–18)
Toxic-metabolic	10	5 (0–23)
Idiopathic	17	9 (3–19)*

* Idiopathic versus mechanical, p = 0.012; versus toxic-metabolic, p = 0.078; versus others, p = 0.009.

DISCUSSION

Although uncommon, AP has gradually become recognized as a manifestation of SLE[31]. This is the largest series reported in the literature. In our patients the diagnosis of AP was established on the basis of clinical symptoms and radiological/surgical confirmation.

Much variability has been recorded on the alleged frequency of AP in SLE patients, varying from 0.2 to 8.2%[14-17,19,39]. This diversity may be explained by inconsistent data collection or misdiagnosis of mild cases[19]. Also, there is a lack of definition of AP[16,17], or deficient inclusion criteria for AP considering only total amylase increase[14,15] without more specific assessment such as pancreatic isoamylase or lipase determinations and/or morphological features. We calculated the prevalence after a careful chart review of all SLE cases diagnosed during a period of 9.5 years. The value of 3.5% that we found is higher than that of AP in the general population (0.5–0.79/1000/year)[40] and is 10 times higher than in the entire number of patient admissions, by such diagnosis, at our institute (2.9–5.6/1000/year)[41].

Table 3. Case-control analysis for etiology, severity, and mortality in AP.

	Cases AP in SLE n = 32 (%)	Controls AP without SLE n = 128 (%)	OR (95% CI)*	p
Etiology				
Mechanical	10 (31)	95 (74)	0.2 (0.4–0.1)	< 0.00001
Toxic-metabolic	7 (23)	15 (12)	2.1 (0.8–5.6)	0.136
Idiopathic	15 (46)	18 (14)	5.4 (2.4–12.1)	< 0.00001
Severity	22 (69)	29 (23)	7.5 (3.4–16.5)	< 0.00001
Mortality	7 (22)	4 (3)	8.6 (2.8–26.9)	0.0002

* OR (95% CI): Odds ratio, 95% confidence interval.

Pancreatitis occurred early in the course of SLE in 40% of patients whose other early manifestations of SLE were otherwise similar to those described in the literature for all SLE patients[42-44]. Thus, the initial clinical picture gave no warning of the potential development of this severe manifestation/complication.

When we segregated the probable cause of AP into the categories[30] recently proposed (mechanical, toxic-metabolic, or idiopathic), we could establish a definite cause in over half the events (58.5%). As in all AP patients[45-47] the most frequent cause was mechanical, due to biliary disease. We also found similar results in our control group but the relative frequency was significantly higher than in SLE cases. The number of episodes associated with a toxic-metabolic factor was similar in both groups. Thus, any of the various causes may be responsible for an AP episode in a patient with SLE and, as such, they should be suspected and studied. This has not been emphasized in previous reports of AP in SLE patients where no systematic search for etiology has been done and discussion has mainly addressed the possible role of SLE or of drugs potentially associated with AP[14,15,17,19].

In the remaining 41% of AP episodes no apparent cause other than SLE was identified. Even if other uncommon AP causes such as genetic alterations, congenital malformations, or infection were not specifically excluded, the frequency of these idiopathic cases was higher in SLE patients than could be expected from previous reports[45-47] and from our own findings in the control group, where only 14% of the episodes could be considered idiopathic. Thus, in the case-control part of our study, the risk for an AP episode to be idiopathic was significantly increased in the SLE group (OR 5.4, 95% CI 2.4–12.1). When we applied a validated index for SLE activity (Mex-SLEDAI)[38] we found significantly higher scores in the idiopathic compared to the other 2 etiological groups. It would therefore appear that SLE activity could be an important cofactor predisposing the pancreas to trigger an abnormal inflammatory response. We suggest that idiopathic AP episodes may be considered a manifestation of SLE, while the remainder could be considered a complication of SLE or its treatment.

Drug toxicity has been a matter of concern as a potential cause of AP, particularly since the report of corticosteroid-associated pancreatitis in rabbits[48]. In SLE patients, the role of corticosteroids is difficult to ascertain due to the natural coexistence of disease activity with high doses of prednisone as well as other drug therapies, some with stronger evidence than corticosteroids for the causation of pancreatitis[30,37]. Moreover, Saab, *et al*[19] published a series of 8 SLE patients with inactive disease whose AP episodes improved biochemically and clinically with an increase in the dose of corticosteroids.

We found no evidence to invoke drugs, including corticosteroids and azathioprine, as a potential cause of idiopathic episodes: in 4 patients (24%), there was no history of drug consumption and high doses of corticosteroids were started. In the remaining patients corticosteroids were increased, as there was clinical evidence of SLE activity measured by means of the Mex-SLEDAI. Objective evidence of response to this therapeutic approach cannot be established in our study because there was no patient in whom corticosteroid treatment was stopped, reduced, or never initiated; however, a deleterious effect of corticosteroids on AP is unlikely because outcome in idiopathic cases was similar to that of other etiologies. Also, no differences in severity were found when idiopathic cases were classified according to history of immunotherapy at AP onset. Further, no patient experienced recurrence when reexposed to drugs as required for control of SLE.

The majority of AP episodes occurring in our SLE patients were classified as severe by the Atlanta criteria[33] and one-fifth of the patients died. We found no differences in the severity or mortality among the various etiological groups. The rate of severe and fatal AP episodes was higher than expected in AP occurring in non-SLE patients, both from the findings in the literature[40] and in our controls. Because successive bouts of AP may be less severe than the first[45], we selected for comparison the first episode of AP in cases and controls. The outcome of AP in SLE found in smaller and selected series has been controversial. Thus, contrary to our findings, Saab, *et al*[19] described neither deaths nor complications in their 8 SLE patients with AP. Reynolds, *et al*[14] reported a low rate of complications (10%) and one death (5%). In agreement with us, DiVittorio, *et al*[15]

reported that 5 out of 7 patients died due to infection, all with multiorgan involvement. The mortality rate of SLE patients with AP in our study is in accord with that reported by Lê Thi Huong, *et al*[17] in their review of 70 cases and by us in a previous series of 26 episodes of AP in 18 SLE patients[49]. Most of our SLE patients' deaths (5/7) were related to multiple organ failure and/or sepsis. In this study, mortality was not related to lupus disease activity or to etiology (data not shown).

The results of our survey of all AP episodes in a population of patients with SLE and the case-control analysis support the role of SLE in increasing the susceptibility for development of AP as well as more severe and frequently fatal episodes.

REFERENCES

1. Reifenstein EC, Reifenstein EC Jr, Reifenstein GH. A variable symptom complex of undetermined etiology with fatal termination. Arch Intern Med 1939;63:553.
2. Paulino-Nelto A, Dreiling DA. Pancreatitis in disseminated lupus erythematosus. A case report. J Mt Sinai Hosp NY 1960;27:291-5.
3. Sparberg M. Recurrent acute pancreatitis associated with systemic lupus erythematosus. Am J Dig Dis 1967;12:522-6.
4. Bruijn JA, van Albada-Kuipers GA, Smit VT, et al. Acute pancreatitis in systemic lupus erythematosus. Scand J Rheumatol 1986;15:363-7.
5. Baron M, Brisson ML. Pancreatitis in systemic lupus erythematosus. Arthritis Rheum 1982;25:1006-9.
6. Nwaneri UR, Callender CO, Stevens JE. Lupus pancreatitis. J Natl Med Assoc 1995;87:575-6.
7. Eaker EY, Toskes PP. Systemic lupus erythematosus presenting initially with acute pancreatitis and a review of the literature. Am J Med Sci 1989;297:38-41.
8. Mekori YA, Yaretzky A, Schneider M, et al. Pancreatitis in systemic lupus erythematosus: a case report and review of the literature. Postgrad Med J 1980;56:145-7.
9. Moalla M, Boussen K, Meddeb S, et al. Fatal acute pancreatitis in systemic lupus erythematosus. Ann Med Interne (Paris) 1991;142:230-2.
10. Wolman R, de Gara C, Isenberg D. Acute pancreatitis in systemic lupus erythematosus: report of a case unrelated to drug therapy. Ann Rheum Dis 1988;47:77-9.
11. Croft SM, Jarrett MP, Craig R, et al. Pancreatitis and systemic lupus erythematosus: a case report. Arthritis Rheum 1983;26:238-9.
12. Takasaki M, Yorimitsu Y, Takahashi I, et al. Systemic lupus erythematosus presenting with drug-unrelated acute pancreatitis as an initial manifestation. Am J Gastroenterol 1995;90:1172-3.
13. Giordano M, Gallo M, Chianese U, et al. Acute pancreatitis as the initial manifestation of systemic lupus erythematosus. Z Rheumatol 1986;45:60-3.
14. Reynolds JC, Inman RD, Kimberly RP, et al. Acute pancreatitis in systemic lupus erythematosus: report of twenty cases and a review of the literature. Medicine (Baltimore) 1982;61:25-32.
15. DiVittorio G, Wees S, Coopman WJ, et al. Pancreatitis in systemic lupus erythematosus [abstract]. Arthritis Rheum 1982;25 Suppl:S6.
16. Vitali C, Bencivelli W, Isenberg DA, et al. Disease activity in systemic lupus erythematosus: report of the Consensus Study Group of the European Workshop for Rheumatology Research. I. A descriptive analysis of 704 European lupus patients. European Consensus Study Group for Disease Activity in SLE. Clin Exp Rheumatol 1992;10:527-39.
17. Le Thi Huong D, Papo T, Laraki R, et al. Pancreatitis in systemic lupus erythematosus. Review of the literature apropos of 5 cases. Rev Med Interne 1994;15:89-94.
18. Padilla B, Pollak VE, Pesce A, et al. Pancreatitis in patients with end-stage renal disease. Medicine (Baltimore) 1994;73:8-20.
19. Saab S, Corr MP, Weisman MH. Corticosteroids and systemic lupus erythematosus pancreatitis: a case series. J Rheumatol 1998;25:801-6.
20. Hebbar M, Gosset D, Hatron PY, et al. Acute pancreatitis, systemic lupus and antiphospholipid syndrome. 2 cases. Rev Med Interne 1994;15:146-7.
21. Vera R. Pancreatitis aguda en el lupus eritematoso generalizado. Rev Gastroenterol Mex 1985;50:161-7.
22. Fries J, Holman H. Systemic lupus erythematosus: a clinical analysis. Philadelphia: W.B. Saunders; 1978.
23. Ropes MW. Systemic lupus erythematosus. Cambridge, MA: Harvard University Press; 1976.
24. Pollak VE, Grove WJ, Kark RM, et al. Systemic lupus erythematosus simulating an acute surgical condition of the abdomen. N Engl J Med 1958;259:258-65.
25. Seifert G, Heinz N, Ruffmann A. Pancreatitis associated with visceral lupus erythematosus. Gastroentererologia 1967;107:317-27.
26. Dreiling DA, Robert J, Toledano AE. Vascular pancreatitis. A clinical entity of growing importance. J Clin Gastroenterol 1988;10:3-6.
27. Wang CR, Hsieh HC, Lee GL, et al. Pancreatitis related to antiphospholipid antibody syndrome in a patient with systemic lupus erythematosus. J Rheumatol 1992;19:1123-5.
28. Serrano-Lopez MC, Yebra-Bango M, Lopez-Bonet E, et al. Acute pancreatitis and systemic lupus erythematosus: necropsy of a case and review of the pancreatic vascular lesions. Am J Gastroenterol 1991;86:764-7.
29. Steinberg W, Tenner S. Acute pancreatitis. N Engl J Med 1994;330:1198-210.
30. Somogyi L, Martin SP, Venkatesan T, et al. Recurrent acute pancreatitis: an algorithmic approach to identification and elimination of inciting factors. Gastroenterology 2001;120:708-17.
31. Petri M. Pancreatitis in systemic lupus erythematosus: still in search of a mechanism. J Rheumatol 1992;19:1014-6.
32. Seelig R, Seelig HP. The possible role of serum complement system in the formal pathogenesis of acute pancreatitis. Acta Hepagastroenterol 1975;22:263-8.
33. Bradley EL. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, GA, September 11-13, 1992. Arch Surg 1993;128:586-90.
34. Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic research. Principles of quantitative methods. New York: Lifetime Learning Publications; 1982.
35. Rutsky EA, Robards M, Van Dyke JA, et al. Acute pancreatitis in patients with end-stage renal disease without transplantation. Arch Intern Med 1986;146:1741-5.
36. Bruno MJ, van Westerloo DJ, van Dorp WT, et al. Acute pancreatitis in peritoneal dialysis and hemodialysis: risk, clinical course, outcome, and possible aetiology. Gut 2000;46:385-9.
37. Runzi M, Layer P. Drug-associated pancreatitis: facts and fiction. Pancreas 1996;13:100-9.
38. Guzman J, Cardiel MH, Arce-Salinas A, et al. Measurement of disease activity in systemic lupus erythematosus. Prospective validation of 3 clinical indices. J Rheumatol 1992;19:1551-8.
39. Dubois EL. Systemic lupus erythematosus. 2nd ed. Los Angeles: UCLA Press; 1974.
40. Toouli J, Brooke-Smith M, Carr-Locke D, et al. Guidelines for the management of acute pancreatitis. J Gastroenterol Hepatol 2002;17 Suppl:S15-39.

41. Robles-Diaz G, Vargas F, Uscanga L, et al. Chronic pancreatitis in Mexico City. Pancreas 1990;5:479-83.
42. Cervera R, Khamashta MA, Font J, et al. Systemic lupus erythematosus: clinical and immunological patterns of disease expression in a cohort of 1000 patients. The European Working Party on Systemic Lupus Erythematosus. Medicine (Baltimore) 1993;72:113-24.
43. Rothfield N. Clinical features of systemic lupus erythematosus. In: Kelly WN, Harris ED, Ruddy S, Sledge CB, editors. Textbook of rheumatology. Philadelphia: W.B. Saunders; 1981:1106-32.
44. Dubois EL, Tuffanelli EL. Clinical manifestations of systemic lupus erythematosus. Computer analysis of 520 cases. JAMA 1964;190:104-11.
45. Appelros S, Borgstrom A. Incidence, aetiology and mortality rate of acute pancreatitis over 10 years in a defined urban population in Sweden. Br J Surg 1999;86:465-70.
46. Suazo-Barahona J, Carmona-Sanchez R, Robles-Diaz G, et al. Obesity: a risk factor for severe acute biliary and alcoholic pancreatitis. Am J Gastroenterol 1998;93:1324-8.
47. Sakorafas GH, Tsiotou AG. Etiology and pathogenesis of acute pancreatitis: current concepts. J Clin Gastroenterol 2000;30:343-56.
48. Stumpf HH, Wilens SL, Somoza C. Pancreatic lesions and peripancreatic fat necrosis in cortisone-treated rabbits. Lab Invest 1956;5:224-5.
49. Hernandez-Cruz B, Pascual-Ramos V, Villa AR, et al. Twenty-six episodes of acute pancreatitis in 18 patients with systemic lupus erythematosus [abstract]. Arthritis Rheum 1998;41 Suppl:S329.