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• BRIEF REPORTS •

Formalized therapeutic guideline for hyperlipidemic severe acute pancreatitis

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Abstract

AIM: To investigate a formalized therapeutic guideline for hyperlipidemic severe acute pancreatitis (HL-SAP).

METHODS: Thirty-two consecutive patients with severe acute pancreatitis were included in the clinical trial. All of them met the following five criteria for admission to the study, namely the Atlanta classification and stratification system for the clinical diagnosis of SAP, APACHEII score more than 8, time interval for therapeutic intervention less than 72 hours after onset of the disease, serum triglyceride (TG) level 6.8 mmol/l or over, and exclusion of other etiologies. They were divided into severe acute pancreatitis group (SAP, 22 patients) and fulminant severe acute pancreatitis group (FSAP, 10 patients). Besides the conventional therapeutic measures, *Penta-association therapy* was also applied in the two groups, which consisted of blood purification (adsorption of triglyceride and hemofiltration), antihyperlipidemic agents (fluvastatin or lipanthyl), low molecular weight heparin (fragmin), insulin, topical application of Pixiao (a traditional Chinese medicine) over the whole abdomen. Serum triglyceride, pro-inflammatory cytokines and anti-inflammatory cytokines were determined before blood purification (PF), at the end of blood purification (AFE) and on the 7th day after onset of the disease (AF7) respectively. Simultaneously, severity of the diseases was assessed by the APACHE II system. Prognosis was evaluated by non-operation cure rate, absorption rate of pseudocyst, time interval pseudocyst absorption, hospital stay and survival rate.

RESULTS: Serum triglyceride level (mmol/L), TNFα (U/ml) concentration and APACHE II score were significantly decreased ($P<0.05$) at AFE and AF7, as compared with PF. However, serum IL-10 concentration (pg/ml) was increased significantly ($P<0.001$) at AFE, and decreased significantly ($P<0.05$) at AF7 when compared with PF. Operations: The First surgical intervention time was 55.8±42.6 days in SAP group (5 patients) and 12.2±6.6 days in FSAP group (7 patients), there was a significant difference between the two groups ($P=0.02$). The number of operations in the two groups was 1.33±0.5 *vs* 3.5±1.2 ($P=0.0037$), respectively. Prognosis: Non-operation cure rate, absorption rate of pseudocyst, hospital stay and survival rate in SAP group and FSAP group were 100 % (22/22) *vs* 11.1 % (1/9), 77.3 % (17/22) *vs* 11.1 % (1/9), 54.2±35.9 *vs* 99.1±49.5 days ($P=0.008$) and 100 % (22/22) *vs* 66.7 % (6/9) ($P=0.0044$). The time for absorption of pseudocyst was 135.1±137.5 days in SAP group.

CONCLUSION: *Penta-association therapy* is an effective guideline in the treatment of hyperlipidemic severe acute pancreatitis at its early stage (within 72 hours).

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INTRODUCTION

Currently, cholilithiasis, alcohol abuse, hyperlipidemia and other specific factors, are the main causues of acute pancreatitis. The morbidity of severe acute pancreatitis secondary to hyperlipidemia (HL) has been apparently increased in recent years, acute pancreatitis occurred in 12-38 % of hyperlipidemic patients[1,2]. Hypertriglyceridemia (HTG) was the second cause of acute pancreatitis in our specialty center. However, this is in contrast with Yadav' s views point[3] that it was a rare cause of severe acute pancreatitis, obviously different from our situation.

Serum triglyceride (TG) level more than 10 to 20 mmol/l in patients with types I, IV, or V hyperlipidemia (Fredrickson' s classification) might lead to acute pancreatitis, so it has been considered as an identifiable risk factor[3]. It was reported that the mechanism leading to severe acute pancreatitis was that combining capacity of albumin surpassed by over production of free fatty acid would cause tissue toxicity. Thus, pancreatic acinar cells and microvessels were injured[4-8]. The main treatment for hyperlipidemic severe acute pancreatitis (HL-SAP) is to decrease serum triglyceride level and to prevent systemic inflammatory response. Although serum triglyceride could be decreased by plasmapheresis[9], there has been no formal therapeutic strategy to treat HL-SAP at present. We retrieved references about the treatment of HL-SAP from MEDLINE during 1966-2003 using severe acute pancreatitis and hyperlipidemia as the key words, and found that reports were all case reports of single treatment measure[10-12]. No formalized therapeutic strategy was found. Therefore, we prospectively treated patients with HL-SAP by *Pent-association therapy* which consisted of purification, antihyperlipidemic agents, insulin, heparin and topical application of Pixiao (a traditional Chinese medicine) over the whole abdomen to observe its therapeutic effects and influence on prognosis.

MATERIALS AND METHODS

Patients and groups

Patient Thirty-two consecutive patients with SAP admitted to Department of Surgical Intensive Care Unit, Ruijin Hospital, Shanghai, China, from April 2000 to March 2003 were included in the clinical trial. Therapeutic strategies to all patients were determined by a group of doctors from SICU and Department of Surgery.

Groups Five entry criteria for admission to the study were the Atalanta classification system to stratify patients with acute

pancreatitis (1992)[13], APACHEII score more than 8, within 72 hours after onset of the disease, serum triglyceride level more than 6.8 mmol/L, and exclusion of other etiologies.

The diagnosis of fulminant severe acute pancreatitis (FSAP) was made according to the following criteria.

FSAP was diagnosed by meeting one or more of the following indices within 72 hours after onset of the disease with adequate fluid resuscitation such as APACHEII score 20 or more, acute renal failure, ARDS, DIC, and Glasgow score less than 8.

According to the aforementioned criteria, 32 patients were divided into SAP group (22 patients) and FSAP group (10 patients). Of the FSAP group, one patient was excluded from the clinical trial due to giving up of the therapy. The patient did not undergo triglyceride adsorption and hemofiltration, and thus developed ARDS and acute renal failure within 48 hours. According to theoretical speculation and references, the *Penta-association therapy* might have some positive effects on patients. Therefore, we did not set control group in the present study. In addition, patients and/or their family were told about the trial in details. We were thus authorized to perform the study.

Etiology This included uncontrolled diabetes mellitus, long period alcohol abuse, heredity, pregnancy, obesity, *etc*. Among them, 23 men aged 45±9.4 years, 9 women aged 41.9±14.9 years.

Methods

Thearpy Conventional therapy: It included appropriate fluid resuscitation, fasting, gastrointestinal decompression, use of pancreatic enzyme inhibitors, prophylactic antibiotics, decoction of raw rhubarb poured into stomach via gastric tube, enteral nutrition and operation if necessary.

Specific therapy (Penta-association therapy) This included blood purification (adsorption of triglyceride and hemofiltration), triglyceride decreasing antihyperlipidemic agents (fluvastatin sodium capsules 40 mg, qn, P.O; lipanthyl, 200 mg qn, P.O), low molecular weight heparin (fragmin 5 000 IU, subcutaneous injection, qd, for 3 days), insulin by intravenous infusion (blood sugar controlled to less than 200 mg/dl), topical application of Pixiao over the whole abdomen.

Adsorption of triglyceride and hemofiltration Blood purification was performed using Diapact CRRT machine (B. Braun Co., Germeny). Polysulfone filters were used (Cut-off-point 30 000 Dalton, AV 600S, Fresenius Medical Care). Systemic anticoagulation was undergone with low molecular weight heparin (fragmin, 5 000 IU/ampule) at a dose of 100-140 IU/kg for bolus injection. Ultrafiltrate was replaced with substitutes made according to patient' s electrolyte and blood glucose. Pre-dilution mode was used. Extracoporeal blood flow ranged from 250 to 360 ml/min. Ultrafiltrating rate was controlled within 50-500 ml/h. In order to remove triglyceride rapidly, we changed the filter every 4 hours.

Indications for stopping blood purification Short veno-venous hemofiltration was stopped when the abdominal symptoms and signs disappeared, or the heart rate was less than 90 beats/min and the respiration rate was 20 times/min, respectively. Continuous veno-venous hemofiltration was stopped if the renal function was recovered and/or heart rate was less than 90 beats/min and the respiration rate was 20 times/min respectively.

Determination of Indices Serum levels of triglyceride, TNFα and IL-10 were determined before blood purification (PF), at the end of therapy (AFE) and on the 7th day (AF7) after onset of the disease. APACHE II scores were evaluated simultaneously. Activity of TNFα was assessed in the L929 cell line. IL-10 was tested using a commercially available ELISA kit (From Endogen Company, USA.).

Follow-up Enhanced CT scan of abdomen was performed every month for the patients with successful conservative treatment, and intra- and extra-pancreatic radiological changes were observed.

Prognosis Non-operation curative rate, survival rate, hospital stay, absorption rate of pseudocyst, time of first operation and total operation time were calculated and compared between the two groups.

Statistics

Data were reported as mean ± standard deviation, and analyzed using Student' s *t* and or chi square test.

RESULTS

Serum level of triglyceride, cytokine and APACHEII score

Serum concentrations of triglyceride and TNFα, and APACHE II scores were significantly decreased at AFE (t=5.687, P<0.001; t=6.342, P<0.001; t=12.12, P<0.001) and AF7 (t=7.576, P<0.001; t=10.19, P<0.001; t=15.09, P<0.001) compared with PF. Serum triglyceride level was decreased to safe range within 10 hours after the beginning of blood purification, and to normal range at AF7 when triglyceride was decreased as well as heparin and insulin were used continuously. But serum level of IL-10 at AFE was significantly increased compared with PF (t=19.21, P<0.001). However, it was significantly decreased (t=9. 87, P<0.001) at AF7 compared to PF.

Thus, serum triglyceride and pro-inflammatory cytokines were decreased, and anti-inflammatory cytokine was increased through blood purification (hemofiltration and adsorption of triglyceride), and severity of the disease was significantly decreased (Table 1).

Table 1 Levels of serum triglyceride, cytokines and APACHE II score

	PF	AFE	AF7
Serum triglyceride (mmol/L)	13.1±8.1	4.5±2.3	2.02±0.83
APACHE II score	18.4±4.4	7.38±2.5	5.8±1.5
TNFα (u/ml)	43.1±12.7	26.3±7.5	17.7±5.6
IL-10 (pg/ml)	72.1±20.0	179.6±23.9	31.2±11.5

Time duration for blood purification and number of filters used

Systemic inflammatory response syndrome (SIRS) was prevented through adsorption of triglyceride and short veno-venous hemofiltration in SAP group, but long time blood purification and/or drainage of large amounts of exudates from abdominal cavity and retroperitoneal space were needed in FSAP group. The number of filters used and time duration for blood purification in SAP group and FSAP group were 2.6±1.3 *vs* 2.9±1.5 h, 6.5 ±2.7 *vs* 48±62 h, respectively.

Surgical intervention

Time interval from onset of the disease to the first operation was significantly longer in SAP group (5 patients) than in FSAP group (7 patients) (t=2.715, P=0.02). Debridement of pancreatic necrosis and internal drainage of pseudocyst were performed in SAP group. Only debridement of pancreatic necrosis was performed in FSAP group, but operation number was more than that in SAP group (t=3.775, P=0.0037). This indicated that *Penta-association therapy* had better results in hyperlipidemic SAP than in FSAP group (Table 2).

Prognosis

We compared the results from this clinical trial with 283 patients treated with conventional therapy in our hospital, and found that non-operation cure rate was 100 %(22/22) in the present

SAP group, and was 43.5 % in our previous group (123/283) (χ^2=26.16, P=3.3×10^{-7}). The survival rate was 100 %(22/22) and was 84.1 % in our previous group (238/283) (χ^2=4.104, P=0.043). In SAP group, pancreatic pseudocysts were resolved spontaneously in 17 patients, with an absorption rate of 77.3 % (17/22), and surgical intervention was thus avoided. Absorption time was 135.1±137.5 days with a variation constant of 102 %.

In FSAP group, only one patient was cured through conservative treatment, its time interval for absorption of pseudocyst was 96 days. Another patient died without operation. Surgical drainage and debridement of pancreatic necrosis were done for the rest of 7 patients within 2 weeks after onset of the disease. The survival rate of 66.7 %(6/9) was slightly higher than 58 % (27/47) from Beger' s report[14] [χ^2=0.2653, P=0.61] without significant difference.

Absorption rate of pseudocyst, non-operation cure rate and survival rate in SAP group were higher than those in FSAP group. Hospital stay was also shortened compared to FSAP group (P=0.008, Table 3).

Table 2 Surgical intervention

	SAP	FSAP
Number of cases	5	7
Time of first operating (days)	55.8±42.6	12.2±6.6
Surgical procedures	Debridement and gastro-or jejuno-pancreatic anastomosis for pseudocyst	Debridement with drainage and nutritional jejunostomy
Number of operation	1.33±0.5	3.5±1.2

Table 3 Prognosis of SAP and FSAP

	SAP group	FSAP group
Number of cases	22	9
Rate of adsorption of pseudocyst	77.3 %(17 / 22)	11.1 %(1 / 9)
Time interval for absorption of pseudocyst	135.1±137.5	96
Non-operation cure rate	100 %(22 / 22)	11.1 %(1 / 9)
Hospital stay (days)	54.2±35.9	99.1±49.5
Survival rate	100 %(22 / 22)	66.7 %(6 / 9)

DISCUSSION

With an increased incidence of hyperlipidemia and its complication, acute pancreatitis also increased accordingly. SAP secondary to hypertriglyceridemia (HTG), presented typically as an episode of SAP, rarely as chronic pancreatitis. A level of serum triglyceride (TG) more than 6.8 mmol/L in patients with types I, IV, or V hyperlipidemia (Fredrickson' s classification) is an identifiable risk factor. The typical clinical profiles of hyperlipidemic pancreatitis were a patient with a preexisting lipid abnormality along with the presence of a secondary factor (e.g., poorly controlled diabetes, alcohol abuse or a medication) that could induce HTG[15]. Patients with isolated hyperlipidemia (type V or I) without a precipitating factor would rarely have pancreatitis. Interestingly, serum pancreatic enzymes might be normal or only minimally elevated even in the presence of SAP as diagnosed by imaging studies. The clinical course of HL-SAP was not different from severe acute pancreatitis caused by other causes. Although conventional management of SAP caused by hyperlipidemia is similar to that by other causes, but it still needs some specific management. So we did this clinical trial to investigate systematically how to manage HL-SAP within 72 hours after onset of the disease.

Formation of therapeutic regimen and its mechanism

At present, there have no formalized therapeutic strategies for the treatment of HL-SAP in the literature, besides single case report or the use of certain measures. In 2000, our Pancreatic Disease Therapy Center considered a therapeutic strategy aiming at HL-SAP that was based on the concepts that hyper-triglyceride, fatty acid and inflammatory mediators were the pathological mechanism of deterioration of HL-SAP[8,16-19]. A prospective investigation was thus carried out. Principles of the strategy included r*apid lowering serum triglyceride, blocking of induction pancreatic damage by pro-inflammatory mediators, preventing recurrence by the use of antihyperlipidemic agents, promoting self- absorption of pancreatic pseudocyst.* Concrete measures could be found in the details of *Penta-association therapy*, which included blood purification (adsorption of triglyceride and hemofiltration), fluvastatin (40 mg, qn, P.O) or lipanthyl (200 mg, qn, P.O), low molecular weight heparin (fragmin, 5 000 IU subcutaneous injection, qd, for three days.), insulin (intravenous infusion, blood sugar level controlled well below 200 mg/dl), and topical application of Pixiao (Chinese traditional medicine) over the whole abdomen. Hyperchylomicronemia caused by hyperlipidemia could lead to not only pulmonary edema[20] and systemic microcirculatory dysfunction, but also release of fatty acids, which would play an important role in causing pancreatic injury[8,17]. Thus, the first item of the therapeutic regimen was adsorption of serum triglyceride, and it was essential to lower blood triglyceride level within the safe range. Simultaneously, heparin could stimulate lipoprotein-lipase activity and accelerate chylomicron degradation[9]. It could also contribute to the decrease of serum triglyceride level. Besides this effect on blood triglyceride, it could also improve microcirculation and prevent activation of neutrophils activity[21]. Polymorphonuclear cells (PMN) could play an important role in the deterioration of severe acute pancreatitis, especially release of elastase (PMNE), which would lead to persistent pancreatic necrosis and acute lung injury[22]. Insulin could not only decrease blood sugar, but also accelerate degradation of chylomicrons[9]. Therefore insulin was given to control blood sugar well below 200 mg/dL. Simultaneously, fluvastatin sodium or lipanthyl was given to decrease blood lipid in order to avoid recurrence of acute pancreatitis.

Though the etiologies of patients with acute pancreatitis could be different, but their pathophysiological changes were just the same[23]. Activated enzymes and oxygen free radicals injured the acinar cells and caused release of cytokines and vasoactive mediators, attracted inflammatory cells and activated vascular endothelium as well as the expression of adhesion molecules. The disturbance of pancreatic microcirculation could induce progression from edematous to necrotizing pancreatitis independent of the early intracellular events, including protease activation. Specific therapy must be directed towards microperfusion failure as the secondary pathogenetic step, since the initial enzyme activation and cytokine release were irreversible by the time of clinical presentation. In experiments comparable to the clinical situation, following therapeutic principles have been proven to be beneficial: increase of blood fluidity, inhibition of leukocyte-endothelium interaction and blockade of systemic inflammatory response. As we know, Short time veno-venous hemofiltration could significantly decrease circulatory TNFα level and increase circulatory IL-10 level[24]. This could block systemic inflammatory response and pancreatic necrosis. Due to dynamic balance of pro-inflammatory and anti-inflammatory cytokines, long time hemofiltration was prohibited to avoid creation of new imbalance in SAP[25]. However, FSAP usually resulted in Ultra-SIRS (systemic inflammatory response syndrome), thus continuous veno-venous hemofiltration and

drainage of abdominal, retroperitoneal toxic exudates were essential to prevent recurrence of Ultra-SIRS. Based on this concept, hemofiltration could be used as a specific measure to treat HL-SAP.

After acute response phase, emphasis should be put on the prevention of infection, rapid subsidence of fluid accumulation in the third space as well as promotion absorption of pancreatic pseudocyst. Topical application of Pixiao (Chinese traditional medicine) over the whole abdomen could ameliorate tissue edema including that of abdominal wall, peritoneum and intestinal wall, and accelerate absorption of pancreatic pseudocyst. Therefore, Pixiao was used through out the whole course of the disease in order to relieve tissue edema and resolve pancreatic pseudocyst spontaneously. When patients were discharged with pancreatic pseudocyst, application of Pixiao was continued until it no longer absorbed fluid and became dry. Though the effect of this measure was slow, but it played an important role in decreasing operation rate.

Efficacy and prognosis

Although *Penta-association therapy* is far from perfect, especially for the prevention of recurrence of the disease, but good clinical efficacy has been obtained by these specific measures in the acute response phase of the episode.

In acute pancreatitis, medications, such as heparin and insulin *etc*. decreased trigylceride levels to less than 10 mmol/L within 2.8 days (1 to 6), the amylase and lipase levels returned to normal after 3 and 4 days respectively, and the abdominal pain was resolved[9,10]. Also, it was reported that plasmapheresis removed blood triglyceride[26-31] and got good results. Clinically, this method could not be propagated to wider use due to the problems of equipments and the need for large amounts of plasma. So we adopted the present measure to adsorb triglyceride. Within 72 hours after onset of the disease, serum triglyceride concentration was decreased to 6.8 mmol/l within 10 hours. At this time, abdominal pain was resolved in 31 patients. So adsorption of triglyceride can not only decrease triglyceride level rapidly, but also resolve abdominal pain and prevent deterioration of the disease. This has been regarded as a necessary measure in the treatment of HL-SAP at its early stage. As to the safe range of blood triglyceride level, it was reported that the level should be decreased to 5.65 mmol/L[32], but in our series when it was below 6.8 mmol/l, abdominal pain in 31 patients was resolved. This discrepancy might be due to different etiologies of hypertriglyceridemia or different preexisting factors. All the patients received insulin, heparin and antilipidemic agents to prevent deterioration of the disease by controlling serum triglyceride level at normal range 7 days after onset of the disease. Even though etiologies resulting in each SAP patients might be different, but pathophysiological lesions were just the same, such as overproduction of cytokines, microcirculation failure and over-activated neutrophils. Therefore, hemofiltration was continued after lipid adsorption to regulate the balance between proinflammatory and anti-inflammatory cytokines. This caused decrease of proinflammatory cytokines as well as temporary increase of anti-inflammatory cytokines with APACHEII score decreased. Our results were in accordance with the report in the literature[24]. Thus, hemofiltration used in the early treatment of HL-SAP was of important clinical significance.

Five patients with SAP underwent the first operation on the 56th day after onset of the disease. Surgical modalities used coincided with literature reports[31]. The major methods were debridement and drainage of pancreatic necrosis as well as internal drainage of pancreatic pseudocyst. But FSAP group underwent the first operation on the 12th day after onset of the disease. The first operation time was earlier than that of SAP group (P<0.01). Surgical methods in FSAP group were mainly debridement and drainage. Furthermore, the number of operations was also increased (P<0.01).

Non-operation cure rate and survival rate were both 100 % in SAP group, they were increased significantly compared with non-operation rate of 43.5 % and survival rate of 84.1 % in 283 patients with SAP in our hospital in the past. Meanwhile, the survival rate of 100 % was higher than that of 62 % (8/13) in literature report[31] [χ^2=9.872, P=0.002]. Incidence of pseudocyst in SAP group was 81.8 % (18/22) which was significantly higher than that of 37 % in literature report of[33]. Pseudocysts in 17 patients resolved spontaneously without operation. The reason why the morbidity and absorption rate of pseudocyst were very high was that the full-blown summit of SAP was at 72 hours, so pancreatic microcirculation was compromised, and ischemia occurred in the pancreas within 72 hours. Thirty-one patients were treated on time within 72 hours, thus pancreatic necrosis was prevented. After onset of the disease, the whole abdomen was covered with Pixiao (rough-wrought Glauber' s salt) until it could not be moistened. This treatment could accelerate absorption of pseudocyst. Ischemia occurred in the major component of Pixiao (rough-wrought Glauber' s salt) is Glauber' s salt, additionally, it contains magnesium sulfate, calcium chloride, magnesium chloride *etc*. and acts on inflammatory mass by the effect of shrinkage, anti-inflammation, dehydration and others. Based on the aforementioned results, we think that *Penta-association therapy* has quite good clinical efficacy, and should be regarded as a specific measure in the treatment of HL-SAP.

HL-FSAP is a sub-type of HL-SAP. Although we applied the same conservative therapeutic measures as those of SAP, but the efficacy was not the same. Only one patient recovered through conservative treatment. It took 96 days for the pseudocyst to resolve spontaneously. Another patient died. If conservative treatment could not control the disease, it was taken as the indication for operation in FSAP. Seven of them underwent debridement and drainage of abdominal and/or retroperitoneal exudates through laparotomy within 2 weeks after onset of the disease. Although its cure rate was 66.7 %, it was still higher than Beger' s 58 %[14] and Bosscha' s 61 %[34], the percentage of mortality was still 33 %. According to our data and literature data[34], survival rate has not been improved through early enthusiastic operation and surgical drainage. This demonstrated that conventional treatment and *Penta-association therapy*, optimal surgical indication, proper timing of operation and choice of drainage method, such as laparoscopy, drainage through single lumen catheter puncture guided by ultrasound, play an important role on survival rate in the treatment of HL-FSAP. Although the viewpoint that conservative treatment should be applied to treat FSAP during it' s early stage (within 2 weeks)[35] was controversial, it is advisable to apply cautiously drainage through laparotomy in the treatment of FSAP during its early stage, and this could achieve curing rate. Some authors suggested that management and clinical surveillance required specific expertise, and management of these patients was best undertaken in specialized centers.

It is thus evident that *Penta-association therapy* upon the basis of conventional therapy for HL-SAP can give good clinical results, but its efficacy in treating FSAP needs to be further improved.

Recommendation of formalized therapeutic regimen

Efforts has been made by the pancreatic disease specialists all over the world in the past hundred years, the therapy of acute pancreatitis has been basically formalized, and therapeutic principles were also basically established. Thus, the cure rate of SAP has reached 80 %. But there were still 20 % of patients who could not be cured. Among them, 15 % were still SAP,

5 % were another subtype - FSAP. Regardless of the etiologies of SAP, their pathophysiological changes were identical, and this determined the accordance of their management. But why there were still 15 % of these patients who could not be cured? Based upon our experimental results, we think some of them were not treated appropriately with regard to their etiologies during early stage (within 72 hours). Although pancreatic lesions could not be prevented from progression even after the etiologies were resolved, continuing existence of the etiological factors would aggravate the disease, such as choledocholithiasis and hyperlipidemia. At present, there are a lot of measures to treat biliary acute pancreatitis, such as EST, ENBD or surgical operation. Nevertheless, there is no formalized regimen to manage HL-SAP. On account of this, our Pancreatic Disease Therapy Center has suggested a formulated specific regimen to treat HL-SAP in order to save some of the 15 % patients. In the present study, from the standpoint of cure rate, almost all the patients were recovered from the disease. Based upon our results, we suggest that it is important to determine whether hyperlipidemia is existent or not by history and laboratory examinations or simply by the presence of chylous blood. Once the diagnosis of HL-SAP is established, besides the conventional therapy, *Penta-association therapy* should be given immediately to mange HL-SAP.

Additionally, 5 % of the patients belonged to FSAP. Although the therapeutic efficacy of HL-FSAP in the present group was somewhat improved, but it was not significant. This should be further investigated.

In summary, HL-SAP has not only the general characteristics of severe acute pancreatitis, but also some specific characteristics. So, besides conventional therapy of SAP, specific strategy should be taken into consideration. *Penta-association therapy* is not a perfect regimen, further refinement, especially to treatment for FSAP, is urgently required.

REFERENCES

1 **Toskes PP.** Hyperlipidemic pancreatitis. *Gastroenterol Clin North Am* 1990; **19:** 783-791
2 **Searles GE,** Ooi TC. Underrecognition of chylomicronemia as a cause of acute pancreatitis. *CMAJ* 1992; **147:** 1806-1808
3 **Yadav D,** Pitchumoni CS. Issues in hyperlipidemic pancreatitis. *J Clin Gastroenterol* 2003; **36:** 54-62
4 **Thompson GR.** Primary hyperlipidaemia. *Br Med Bull* 1990; **46:** 986-1004
5 **Havel RJ.** Pathogenesis, differentiation and management of hypertriglyceridemia. *Adv Intern Med* 1969; **15:** 117-154
6 **Nagai H,** Henrich H, Wunsch PH, Fischbach W, Mossner J. Role of pancreatic enzymes and their substrates in autodigestion of the pancreas. *In vitro* studies with isolated rat pancreatic acini. *Gastroenterol* 1989; **96:** 838-847
7 **Kimura W,** Mossner J. Role of hypertriglyceridemia in the pathogenesis of experimental acute pancreatitis in rats. *Int J Pancreatol* 1996; **20:** 177-184
8 **Domschke S,** Malfertheiner P, Uhl W, Buchler M, Domschke W. Free fatty acids in serum of patients with acute necrotizing or edematous pancreatitis. *Int J Pancreatol* 1993; **13:** 105-110
9 **Berger Z,** Quera R, Poniachik J, Oksenberg D, Guerrero J. Heparin and insulin treatment of acute pancreatitis caused by hypertriglyceridemia. Experience of 5 cases. *Rev Med Chil* 2001; **129:** 1373-1378
10 **Henzen C,** Rock M, Schnieper C, Heer K. Heparin and insulin in the treatment of acute hypertriglyceridemia-induced pancreatitis. *Schweiz Med Wochenschr* 1999; **129:** 1242-1248
11 **Routy JP,** Smith GH, Blank DW, Gilfix BM. Plasmapheresis in the treatment of an acute pancreatitis due to protease inhibitor-induced hypertriglyceridemia. *J Clin Apheresis* 2001; **16:** 157-159
12 **Lechleitner M,** Ladner E, Seyr M, Hoppichler F, Foger B, Hackl JM. Hypertriglyceridemia and acute pancreatitis. *Acta Med Austriaca* 1994; **21:** 125-128
13 **Bradley EL 3rd.** A clinically based classification system for acute pancreatitis. Summary of the international symposium on acute pancreatitis. Atlanta, Ga, September 11 through 13, 1992. *Arch Surg* 1993; **128:** 586-590
14 **Isenmann R,** Rau B, Beger HG. Early severe acute pancreatitis: characteristics of a new subgroup. *Pancreas* 2001; **22:** 274-278
15 **Pfau J.** Acute pancreatitis and hypertriglyceridemia. *Rev Med Chil* 1989; **117:** 907-909
16 **Saharia P,** Margolis S, Zuidema GD, Cameron JL. Acute pancreatitis with hyperlipemia: studies with an isolated perfused canine pancreas. *Surgery* 1977; **82:** 60-67
17 **Hofbauer B,** Friess H, Weber A, Baczako K, Kisling P, Schilling M, Uhl W, Dervenis C, Buchler MW. Hyperlipaemia intensifies the course of acute oedematous and acute necrotising pancreatitis in the rat. *Gut* 1996; **38:** 753-758
18 **Norman J.** The role of cytokines in the pathogenesis of acute pancreatitis. *Am J Surg* 1998; **175:** 76-83
19 **Van Laethem JL,** Eskinazi R, Louis H, Rickaert F, Robberecht P, Deviere J. Multisystemic production of interleukin 10 limits the severity of acute pancreatitis in mice. *Gut* 1998; **43:** 408-413
20 **Warshaw AL,** Lesser PB, Rie M, Cullen DJ. The pathogenesis of pulmonary edema in acute pancreatitis. *Ann Surg* 1975; **182:** 505-510
21 **Capecchi PL,** Ceccatelli L, Laghi Pasini F, Di Perri T. Inhibition of neutrophil function in vitro by heparan sulfate. *Int J Tissue React* 1993; **15:** 71-76
22 **Mao EQ,** Han TQ, Tang YQ, Zhang SD, Zhang SD. Polymorphonuclear elastase is the major causative factor in acute lung injury complicating severe acute pancreatitis in rats. *Zhonghua Xiaohua Zazhi* 1998; **18:** 207-209
23 **Klar E,** Werner J. New pathophysiologic knowledge about acute pancreatitis. *Chirurg* 2000; **71:** 253-264
24 **Mao E,** Tang Y, Han T, Zhai H, Yuan Z, Yin H, Zhang S. Effects of short veno-venous hemofiltration on severe acute pancreatitis. *Zhonghua Waike Zazhi* 1999; **37:** 141-143
25 **Mao EQ,** Tang YQ, Zhang SD. Effects of time interval for hemofiltration on the prognosis of severe acute pancreatitis. *World J Gastroenterol* 2003; **9:** 373-376
26 **Perrone G,** Critelli C. Severe hypertriglyceridemia in pregnancy. A clinical case report. *Minerva Ginecol* 1996; **48:** 573-576
27 **Mayan H,** Gurevitz O, Mouallem M, Farfel Z. Multiple spurious laboratory results in a patient with hyperlipemic pancreatitis treated by plasmapheresis. *Isr J Med Sci* 1996; **32:** 762-766
28 **Majlis S,** Anguita T, Weishaupt R, Socias M. Plasmapheresis in acute pancreatitis secondary to familial hyperlipidemia in a pregnant woman. *Rev Med Chil* 1989; **117:** 1275-1278
29 **Schranz W,** Bartels O. Early plasma exchange in acute pancreatitis. A successful therapeutic principle in extreme hyperlipidemia. *Fortschr Med* 1986; **104:** 530-532
30 **Sunamura M,** Yamauchi H, Takeda K, Suzuki T, Abe R, Oikawa S, Sano R. A case of acute pancreatitis associated with hyperlipidemia and pregnancy with reference to plasma exchange as a therapeutic intervention. *Nippon Shokakibyo Gakkai Zasshi* 1985; **82:** 2139-2143
31 **Ohmoto K,** Neishi Y, Miyake I, Yamamoto S. Severe acute pancreatitis associated with hyperlipidemia: report of two cases and review of the literature in Japan. *Hepatogastroenterology* 1999; **46:** 2986-2990
32 **Nair S,** Yadav D, Pitchumoni CS. Association of diabetic ketoacidosis and acute pancreatitis: observations in 100 consecutive episodes of DKA. *Am J Gastroentero l* 2000; **95:** 2795-2800
33 **Fortson MR,** Freedman SN, Webster PD 3rd. Clinical assessment of hyperlipidemic pancreatitis. *Am J Gastroenterol* 1995; **90:** 2134-2139
34 **Bosscha K,** Hulstaert PF, Hennipman A, Visser MR, Gooszen HG, van Vroonhoven TJ, vd Werken C. Fulminant acute pancreatitis and infected necrosis: results of open management of the abdomen and "planned" reoperations. *J Am Coll Surg* 1998; **187:** 255-262
35 **Gronroos JM,** Nylamo EI. Mortality in acute pancreatitis in Turku University Central Hospital 1971-1995. *Hepatogastroenterology* 1999; **46:** 2572-2574

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