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Transition of early-phase treatment for acute pancreatitis: An analysis of nationwide epidemiological survey

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Abstract

Treatment of acute pancreatitis (AP) is one of the critical challenges to the field of gastroenterology because of its high mortality rate and high medical costs associated with the treatment of severe cases. Early-phase treatments for AP have been optimized in Japan, and clinical guidelines have been provided. However, changes in early-phase treatments and the relationship between treatment strategy and clinical outcome remain unclear. Retrospective analysis of nationwide epidemiological data shows that time for AP diagnosis has shortened, and the amount of initial fluid resuscitation has increased over time, indicating the compliance with guidelines. In contrast, prophylactic use of broad-spectrum antibiotics has emerged. Despite the potential benefits of early enteral nutrition, its use is still limited. The roles of continuous regional arterial infusion in the improvement of prognosis and the prevention of late complications are uncertain. Furthermore, early-phase treatments have had little impact on late-phase complications, such as walled-off necrosis, surgery requirements and late (> 4 w) AP-related death. Based on these observations, early-phase treatments for AP in Japan have approached the optimal level, but late-phase complications have become concerning issues. Early-phase treatments and the therapeutic strategy for late-phase complications both need to be optimized based on firm clinical evidence and cost-effectiveness.

Key words: Diagnostic time; Fluid resuscitation; Enteral nutrition; Continuous regional arterial infusion; Walled-off necrosis

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Core tip: We analyzed past nationwide epidemiological survey data for acute pancreatitis (AP) to assess the trend in early-phase treatments and late complications.

Early-phase treatments for AP in Japan have improved in line with clinical guidelines, but several points still need attention. In addition, early-phase treatments have had little impact on late complications and clinical outcomes, suggesting that an optimized strategy for late complications is still needed.

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INTRODUCTION

Acute pancreatitis (AP) is one of the primary reasons for hospitalization in the field of gastroenterology^[1], and a substantial number of AP cases progress to severe AP, which is accompanied by organ failure^[2]. This condition can be fatal, and therefore multiple severity assessment strategies have been developed worldwide, including in Japan^[3]. To assess the detailed clinical features of AP in Japanese patients, nationwide epidemiological surveys have been conducted^[4-6]. These surveys consisted of a first survey that involved estimating the number of AP patients by stratified random sampling and a second survey that involved the collection of detailed clinical characteristics regarding patients with AP. According to the latest epidemiological survey for AP in Japan, the number of patients with AP is still increasing; there were over 60000 patients in 2011^[4]. Based on previous studies, incident of AP varies among countries^[7,8]. The overall mortality rate of AP has lowered to 2.6%, but in case of severe AP, the mortality rate remains at 10.1%, according to the 2011 survey^[4]. Since around 1500 AP-related deaths are expected annually in Japan, clinical factors and early-phase treatments associated with AP outcome need to be identified.

Recent reports suggest that a patient's condition on admission or during the early-phase can predict AP severity, such as organ failure. For example, elevated serum triglycerides within 72 h of presentation are independently associated with organ failure^[9]. This correlation was also confirmed in the 2011 survey data^[10]. Similarly, patients with AP and disseminated intravascular coagulation or elevated D-dimer on admission were accompanied with a higher organ failure ratio and mortality rate^[11,12]. We previously assessed the past nationwide survey data to identify any trends in the management of AP, and confirmed that the treatment strategy for late complications has shifted to less-invasive, step-up approaches in the last decade^[13]. However, clinical factors that determine late-phase complications have not yet been identified.

Table 1 Required time for acute pancreatitis diagnosis *n* (%)

	2003 Survey	2007 Survey	2011 Survey	<i>P</i> value
Time for diagnosis (Total AP)				
≤ 12 h	707 (51.6)	806 (58.8)	1148 (61.7)	< 0.0001 ¹
13-24 h	288 (21.0)	252 (18.4)	359 (19.3)	
25-48 h	156 (11.4)	150 (10.9)	195 (10.5)	
49-72 h	95 (6.9)	70 (5.1)	69 (3.7)	
≥ 73 h	124 (9.1)	94 (6.8)	89 (4.8)	
Time for diagnosis (Severe AP)				
≤ 12 h	148 (53.1)	170 (60.9)	240 (66.8)	0.003 ¹
13-24 h	54 (19.3)	51 (18.3)	71 (19.8)	
25-48 h	35 (12.5)	31 (11.1)	25 (7.0)	
49-72 h	20 (7.2)	15 (5.4)	13 (3.6)	
≥ 73 h	22 (7.9)	12 (4.3)	10 (2.8)	

¹ χ^2 test. AP: Acute pancreatitis.

Benefits of early-phase treatments in the prevention of late-phase complications also need to be ascertained. In addition, changes in early-phase AP treatments in the last decade might elucidate potential clinical problems that need to be solved. To address this issue, we performed retrospective analysis of the results to nationwide epidemiological surveys. These surveys were conducted mainly by the Research Committee of Intractable Pancreatic Diseases, under the support of the Ministry of Health, Labour, and Welfare of Japan in 2003, 2007, and 2011^[4-6]. In this editorial, we review anonymous data of the clinical-epidemiological characteristics of AP, as collected by postal surveys. Clinical data of 2694 patients in the 2011 survey, 2256 patients in the 2007 survey, and 1779 patients in the 2003 survey were assessed^[4-6]. This study was approved by the Ethics Committee of Tohoku University Graduate School of Medicine (article#: 2015-1-519).

IMPROVEMENT OF REQUIRED TIME FOR AP DIAGNOSIS

In 2003 survey, 84.0% of total AP cases were diagnosed within 48 h. This ratio significantly increased with time, reaching 91.5% in the 2011 survey (Table 1). The ratio of patients diagnosed later than 72 h was 9.1% in the 2003 survey, which decreased to 4.8% in the 2011 survey. This trend was similar in patients with severe AP; 93.6% of severe AP cases were diagnosed within 48 h in the 2011 survey, compared to 84.9% in the 2003 survey (Table 1). These results suggest that the required time for AP diagnosis in Japan has improved in the last decade. Current Japanese guidelines for the management of AP recommend serum lipase or amylase measurements and imaging studies [computed tomography (CT), ultrasonography (US) or magnetic resonance imaging

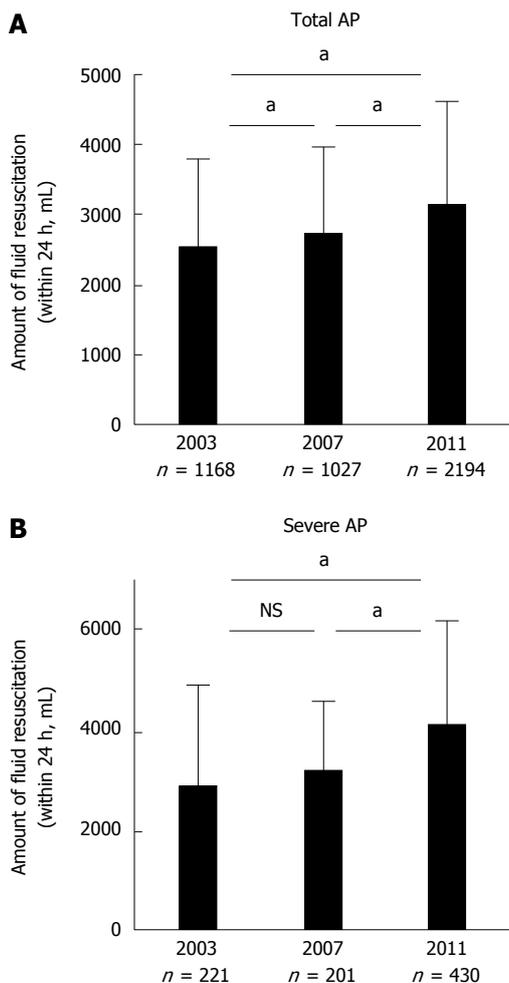


Figure 1 Average amount of fluid resuscitation. A: Average amount of fluid resuscitation within 24 h after admission for total acute pancreatitis (AP) patients. Error bar shows standard deviation. ^a*P* < 0.01; B: Average amount of fluid resuscitation within 24 h after admission for severe AP patients. Error bar shows standard deviation. ^a*P* < 0.01.

(MRI)] for the diagnosis of AP^[14], as well as severity assessment using the revised severity scoring system of AP (2008)^[15,16]. Immediate transfer of patients with severe AP to an adequate facility capable of providing suitable treatment is also recommended^[14]. Awareness of these principles in Japan might be the reason for the improved diagnosis time of AP.

INCREASED AMOUNT OF INITIAL FLUID RESUSCITATION VOLUME

Fluid resuscitation is an essential initial therapy for AP. The Japanese guidelines recommend extracellular solution, such as Ringer’s Lactate solution^[14]. Even though there was no benefit in use of Ringer’s Lactate over normal saline in one study^[17], further validation is necessary to establish the best fluid resuscitation strategy. A previous report pointed out that the amount of fluid volume administered in 48 h to patients with AP admitted into intensive care units

Table 2 Prophylactic administration of antibiotics within 24 h n (%)

	2003 survey	2007 survey	2011 survey	<i>P</i> value
Antibiotics (Total AP)				
Carbapenem	280 (27.7)	327 (32.5)	689 (36.9)	< 0.0001 ¹
Cephem	270 (26.7)	264 (26.2)	485 (26.0)	
Cephem/β-lactamase inhibitor combination	429 (42.4)	390 (38.8)	641 (34.4)	
Others	33 (3.2)	25 (2.5)	51 (2.7)	
Antibiotics (Severe AP)				
Carbapenem	86 (41.2)	107 (52.2)	286 (67.3)	< 0.0001 ¹
Cephem	54 (25.8)	36 (17.6)	48 (11.3)	
Cephem/β-lactamase inhibitor combination	62 (29.7)	57 (27.8)	80 (18.8)	
Others	7 (3.3)	5 (2.4)	11 (2.6)	

¹χ² test. AP: Acute pancreatitis.

(ICU) was significantly less in non-survivors than in survivors^[18]. A faster ratio of fluid resuscitation lowered the mortality rate of AP patients, according to another report^[19]. Average fluid resuscitation for all AP patients within 24 h after admission was 2538.5 ± 1256.1 mL in 2003, 2725.4 ± 1232.1 mL in 2007, and 3145.1 ± 1475.2 mL in 2011, respectively (Figure 1A). Average fluid resuscitation for patients with severe AP within 24 h after admission was 2885.2 ± 1989.1 mL in 2003, 3175.6 ± 1391.0 mL in 2007 and 4103.7 ± 2063.3 mL in 2011, respectively (Figure 1B). Current Japanese guidelines for the management of AP describe the detailed fluid resuscitation strategy as an initial therapy^[14], and this therapeutic concept has been widely accepted in Japan.

TREND IN PROPHYLACTIC ADMINISTRATION OF ANTIBIOTICS

Usage of prophylactic antibiotics for AP treatment is still a matter of debate. Japanese guidelines for the management of AP state that prophylactic administration may improve the prognosis of severe or necrotizing pancreatitis^[14], but another report indicated that prophylactic administration does not affect mortality^[20]. Current retrospective analysis identified increasing use of carbapenem for AP treatment in the last decade, especially in the case of severe AP (Table 2). Carbapenem-resistant bacteria are a serious danger to health, and this resistance is partly promoted by a patient’s prior use of carbapenem^[21]. This fact highlights that the strategy for the use of antibiotics in Japan still needs to be optimized. Continuous administration of antibiotics for more than 2 wk is not recommended in patients without signs of infection, according to Japanese guidelines^[14]. Similarly, prophylactic administration for mild pancreatitis is stated as unnecessary, and these guidelines should be followed.

Table 3 Enteral nutrition *n* (%)

Enteral nutrition	2007 survey	2011 survey	<i>P</i> value
(Total AP)			
Yes	72 (4.7)	135 (6.2)	0.051
No	1466 (95.3)	2053 (93.8)	
Enteral nutrition	2007 survey	2011 survey	<i>P</i> value
(Severe AP)			
Yes	45 (14.6)	97 (22.4)	0.008 ¹
No	264 (85.4)	337 (77.6)	
Enteral nutrition	< 500 beds	500 beds or more	<i>P</i> value
(Severe AP in 2011 survey)			
Yes	14 (9.9)	83 (28.4)	< 0.0001 ¹
No	127 (90.1)	209 (71.6)	

¹ χ^2 test. AP: Acute pancreatitis.

INCREASED USAGE OF ENTERAL NUTRITION IN SEVERE AP

Usage of enteral nutrition for treatment of severe AP in the 2011 survey was significantly increased, compared with the 2007 survey (Table 3). Patients with severe AP treated in hospitals with 500 beds or more were treated with enteral nutrition more frequently than patients treated in hospitals with less than 500 beds (Table 3). Since enteral nutrition is associated with fewer infection-related complications and with length of hospital stay^[22], its efficacy needs to be more widely recognized and a detailed procedure for its routine use needs to be produced. The optimal time to start enteral nutrition is within 48 h of admission, according to the Japanese guidelines^[14]. This recommendation is based on the result of a meta-analysis that identified the superiority of early (within 48 h) enteral nutrition over late enteral nutrition or total parenteral nutrition^[23]. In patients with severe AP not having severe ileal or intestinal ischemia, addition of enteral nutrition should be considered as an initial therapy.

TREND IN CONTINUOUS REGIONAL ARTERIAL INFUSION AND MORTALITY

Continuous regional arterial infusion (CRAI) has developed for the improvement of regional inflammation and infection in the pancreas, by trans-arterial administration of antibiotics and protease inhibitor. Its therapeutic efficacy in Japan has been reported^[24]. Previous study reported an effectiveness of CRAI in randomized controlled study^[25]. CRAI was performed in 18.0% of all AP patients and 22.4% of severe AP patients in the 2003 survey (Table 4). This ratio significantly decreased in the later surveys, with 4.5 and 4.3% for all AP patients, and 14.6 and 17.2% for severe AP patients, in 2007 and 2011 respectively (Table 4). The decrease in the CRAI ratio during this decade might have been due to the discretion, excluding patients without less-enhanced region in the pancreas based on the contrast-enhanced CT

Table 4 Trend in continuous regional arterial infusion *n* (%)

	2003 survey	2007 survey	2011 survey	<i>P</i> value
CRAI (Total AP)				
Yes	118 (18.0)	72 (4.5)	95 (4.3)	< 0.0001 ¹
No	538 (82.0)	1530 (95.5)	2129 (95.7)	
CRAI (Severe AP)				
Yes	72 (22.4)	51 (14.6)	76 (17.2)	0.027 ¹
No	249 (77.6)	299 (85.4)	365 (82.8)	

¹ χ^2 test. CRAI: Continuous regional arterial infusion; AP: Acute pancreatitis.

Table 5 Continuous regional arterial infusion and mortality

CRAI (Severe AP)	2003 survey Mortality	2007 survey Mortality	2011 survey Mortality
Yes	15/71 (21.1)	5/49 (10.2)	7/74 (9.5)
No	23/238 (9.7)	27/279 (9.7)	35/327 (10.7)
<i>P</i> value	0.0098 ¹	0.909	0.752

¹ χ^2 test. CRAI: Continuous regional arterial infusion; AP: Acute pancreatitis.

findings. CRAI might have been limited to patients with severe AP accompanied with lesions that were less enhanced in the CT scan or with necrosis in the pancreas. The mortality rate of patients with severe AP who received CRAI was also assessed. In the 2003 survey, the mortality of patients who received CRAI was significantly higher than that of patients who did not receive CRAI (Table 5). This difference was not significant in the 2007 and 2011 surveys. A recent retrospective multicenter study also reported that CRAI has no efficacy in the treatment of severe AP^[26], which is in agreement with the current observation. These results indicate that further assessment of the efficacy and cost-effectiveness of CRAI is needed before the standard therapeutic strategy is defined.

FACTORS AFFECTING WALLED-OFF NECROSIS DEVELOPMENT, A PATIENT'S NEED FOR SURGERY, AND LATE (> 4 W) AP-RELATED DEATH IN SEVERE AP

To identify the specific effects of early-phase treatments on severe AP-related complications and clinical outcomes, factors were assessed that affected walled-off necrosis (WON) development, a patient's need for surgery, and late phase (later than 4 w after onset of AP) AP-related death, in the 2011 survey. Diagnosis within 48 h, average amount of fluid resuscitation, and CRAI did not affect WON development (Table 6). Enteral nutrition was more frequently performed in patients who developed WON. Patients with severe AP who underwent surgery had been provided significantly more fluid resuscitation and enteral nutrition, while CRAI failed to show any preventive effect (Table 7). Late AP-related death was less prevalent in patients diagnosed within 48 h, but

Table 6 Factors affecting walled-off necrosis development in severe acute pancreatitis in 2011 survey

	WON (+)	WON (-)	P value
Diagnosis within 48 h	14/17 (82.4)	60/63 (95.2)	0.074
Average amount of fluid resuscitation (mL)	4865.8 ± 2130.2	4661.1 ± 2758.3	0.765
Enteral nutrition	14/22 (63.6)	24/72 (33.3)	0.011 ¹
CRAI	11/23 (47.8)	21/75 (28.0)	0.076

¹ χ^2 test. CRAI: Continuous regional arterial infusion; WON: Walled-off necrosis.

Table 7 Factors affecting surgery requirement in severe acute pancreatitis in 2011 survey

	Surgery (+)	Surgery (-)	P value
Diagnosis within 48 h	16/18 (88.9)	279/300 (94.6)	0.513
Average amount of fluid resuscitation (mL)	6183.6 ± 4109.5	4203.1 ± 2810.6	0.003 ¹
Enteral nutrition	13/25 (52.0)	76/350 (21.7)	0.0006 ²
CRAI	8/25 (32.0)	62/360 (17.2)	0.064

¹t-test; ² χ^2 test. CRAI: Continuous regional arterial infusion.

Table 8 Factors affecting late (> 4W) acute pancreatitis-related death in severe acute pancreatitis in 2011 survey

	AP-related death (> 4W)	Alive	P value
Diagnosis within 48 h	5/8 (62.5)	286/305 (98.3)	0.013 ¹
Average amount of fluid resuscitation (mL)	5525.0 ± 3415.5	4295.5 ± 2914.7	0.154
Enteral nutrition	6/12 (50.0)	85/354 (24.0)	0.081
CRAI	0/12 (0.0)	76/355 (21.4)	0.138

¹Fisher's exact test. CRAI: Continuous regional arterial infusion.

the amount of fluid resuscitation, enteral nutrition, and CRAI had little effects (Table 8). These results might be confounded by illness severity, since special therapies such as CRAI or enteral nutrition were possibly performed for the more severe cases. The efficacy of these treatments for the prevention of late complications needs to be assessed by prospective studies observing patients matched for severity. On the other hand, late complications might not be related to the early-phase treatment for AP. If this is correct, the refinement of current therapeutic strategies, such as step-up approaches for WON^[27,28] and less-invasive endoscopic necrosectomy^[29], will be the best way to improve the prognosis of severe AP.

CONCLUSION

Current retrospective analysis identified an improvement over the last decade in the length of time it takes to receive a diagnosis of AP and in the performance of fluid resuscitation. These results indicate good recognition of the guidelines for the management of

AP. However, prophylactic administration of broad-spectrum antibiotics for AP has been widespread in Japan, and this needs to be reversed. Use of enteral nutrition is still limited, and needs to be practiced more routinely. The efficacy of CRAI has been a matter of debate in the last decade, and the current study did not reveal any clear efficacy of CRAI in AP treatment. This result is in agreement with a recent study^[22]. In addition, early-phase treatments have little impact on late complications, such as WON, a patient's need for surgery, and late AP-related death. The efficacy of special treatments such as CRAI and enteral nutrition for the prevention of late complications needs further validation, but if these are not especially effective, refinement of therapeutic approaches will be necessary for the improvement of prognosis. In conclusion, both early-phase treatments and late-phase interventions for AP need to be optimized based on firm evidence and cost-effectiveness.

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