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JPN Guidelines for the management of acute pancreatitis: epidemiology, etiology, natural history, and outcome predictors in acute pancreatitis

Miho Sekimoto[1], Tadahiro Takada[2,*], Yoshifumi Kawarada[3], Koichi Hirata[4], Toshihiko Mayumi[5], Masahiro Yoshida[2], Masahiko Hirota[6], Yasutoshi Kimura[4], Kazunori Takeda[7], Shuji Isaji[8], Masaru Koizumi[9], Makoto Otsuki[10,**], and Seiki Matsuno[11,***]

[1] Department of Healthcare Economics and Quality Management, Kyoto University Graduate School of Medicine, Konoe-cho, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan
[2] Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan
[3] Ueno Municipal Hospital, Mie, Japan
[4] First Department of Surgery, Sapporo Medical University School of Medicine, Hokkaido, Japan
[5] Department of Emergency and Critical Care Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan
[6] Department of Gastroenterological Surgery, Kumamoto University Graduate School of Medical Science, Kumamoto, Japan
[7] Department of Surgery, National Hospital Organization Sendai Medical Center, Sendai, Japan
[8] Department of Hepatobiliary Pancreatic Surgery and Breast Surgery, Mie University Graduate School of Medicine, Mie, Japan
[9] Ohara Medical Center Hospital, Fukushima, Japan
[10] Department of Gastroenterology and Metabolism, University of Occupational and Environmental Health, Japan, School of Medicine, Kitakyushu, Japan
[11] Division of Gastroenterological Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan

Abstract
Acute pancreatitis is a common disease with an annual incidence of between 5 and 80 people per 100000 of the population. The two major etiological factors responsible for acute pancreatitis are alcohol and cholelithiasis (gallstones). The proportion of patients with pancreatitis caused by alcohol or gallstones varies markedly in different countries and regions. The incidence of acute alcoholic pancreatitis is considered to be associated with high alcohol consumption. Although the incidence of alcoholic pancreatitis is much higher in men than in women, there is no difference in sexes in the risk involved after adjusting for alcohol intake. Other risk factors include endoscopic retrograde cholangiopancreatography, surgery, therapeutic drugs, HIV infection, hyperlipidemia, and biliary tract anomalies. Idiopathic acute pancreatitis is defined as acute pancreatitis in which the etiological factor cannot be specified. However, several studies have suggested that this entity includes cases caused by other specific disorders such as microlithiasis. Acute pancreatitis is a potentially fatal disease with an overall mortality of 2.1%–7.8%. The outcome of acute pancreatitis is determined by two factors that reflect the severity of the illness: organ failure and pancreatic necrosis. About half of the deaths in patients with acute pancreatitis occur within the first 1–2 weeks and are mainly attributable to multiple organ dysfunction syndrome (MODS). Depending on patient selection, necrotizing pancreatitis develops in approximately 10%–20% of patients and the mortality is high, ranging from 14% to 25% of these patients. Infected pancreatic necrosis develops in 30%–40% of patients with necrotizing pancreatitis and the incidence of MODS in such patients is high. The recurrence rate of acute pancreatitis is relatively high: almost half the patients with acute alcoholic pancreatitis experience a recurrence. When the gallstones are not treated, the risk of recurrence in gallstone pancreatitis ranges from 32% to 61%. After recovering from acute pancreatitis, about one-third to one-half of acute pancreatitis patients develop functional disorders, such as diabetes mellitus and fatty stool; the incidence of chronic pancreatitis after acute pancreatitis ranges from 3% to 13%. Nevertheless, many reports have shown that most patients who recover from acute pancreatitis regain good general health and return to their usual daily routine. Some authors have emphasized that endocrine function disorders are a common complication after severe acute pancreatitis has been treated by pancreatic resection.

Key words Pancreatitis · Epidemiology · Etiology · Survival rate · Treatment outcome

Offprint requests to: M. Sekimoto
* President, Japanese Society of Emergency Abdominal Medicine; President, Japanese Society of Hepato-Biliary-Pancreatic Surgery; President, Asian-Pacific Hepato-Pancreato-Biliary Association
** Chairman, Intractable Pancreatic Disease Investigation and Research Group of the Japanese Ministry of Health, Labour and Welfare
*** President, Japan Pancreas Society

Clinical questions

1. **What is the incidence of acute pancreatitis? Is it different for different countries and areas?**
2. **What are the causes of acute pancreatitis?**
3. **What are the risk factors for developing acute pancreatitis?**
4. **What are the outcomes of acute pancreatitis?**

Introduction

The Japanese Society for Emergency Abdominal Medicine, the Japanese Society of Hepato-Biliary-Pancreatic Surgery, and the Japan Pancreas Society have developed evidence-based clinical practice guidelines for acute pancreatitis that integrate all available evidence regarding the epidemiology and clinical management of acute pancreatitis published between 1960 and 2000.[1] In this article we have added a review of articles published since 2000, and we describe the epidemiology, etiology, natural history, and predictors of disease outcome in acute pancreatitis.

Clinical questions (CQ) 1. What is the incidence of acute pancreatitis? Is it different for different countries and areas?

Studies on the incidence of acute pancreatitis show large regional differences. Although the diagnostic criteria for acute pancreatitis vary for different countries, regions, and reports, those reports published since 2000 have revealed that the annual incidence rates of acute pancreatitis range from 5 to 80 per 100000 (Table 1). Many studies of trends in the incidence of acute pancreatitis have suggested that the numbers have been increasing in recent years.[8,9]

The first national survey in Japan was conducted in 1987 by the Research Group for Acute Pancreatitis and was organized by the Japanese Ministry of Health and Welfare. The survey targeted patients treated for acute pancreatitis between 1982 and 1986 at medical institutions selected by a stratified random sampling method. According to the survey, the number of acute pancreatitis patients in Japan was estimated to be 14500/year [95% confidence interval (CI): 9500–19500] and the estimated incidence of acute pancreatitis was 12.1/100000. The second national survey estimated that the number of patients in 1998 was 19500 (95% CI: 17000–22000) and the incidence was 15.4/100000 (20.5/100000 for men and 10.6/100000 for women). The ratio of men to women was 1.9 to 1 and incidence peaked in the 7th decade of life in men and in the 8th decade in women (Fig. 1). Although the two surveys differed in terms of their subjects and methods of estimation, the incidence of acute pancreatitis is considered to be increasing (evidence level; Level 4).[10] Epidemiological studies in Japan have encountered the following problems: the definition of acute pancreatitis in Japan includes acute exacerbations of chronic pancreatitis and the data are hospital-based and exclude autopsy cases. Nevertheless, the incidence of acute pancreatitis in Japan is generally considered to be below the average level found in other countries.

Table 2 summarizes the results of the national survey conducted in 1998. Severe acute pancreatitis accounted for 10.3% of all acute pancreatitis cases in the first survey and 25.3% in the second survey.[11–13] However, it cannot be concluded from these statistics that the incidence of severe acute pancreatitis has increased, because different criteria were used to evaluate the severity of acute pancreatitis in the two surveys.

CQ2. What are the causes of acute pancreatitis?

The two major etiological factors responsible for acute pancreatitis are alcohol and cholelithiasis (gallstones).[2] The proportions of pancreatitis attributed to alcohol and gallstones in all cases of acute pancreatitis vary considerably for different countries and regions (Table 3).[3–7,16,17] In Hungary, the incidence of alcoholic pancreatitis is two and a half times that of gallstone pancreatitis,[14] and the high incidence of acute alcoholic

Table 1. Incidence of acute pancreatitis

Author (year)	Country/region	Subjects	Incidence (per 100000/year)
Banks[2] (2002)	England, the Netherlands	First attack/recurrence	5–10
	Scotland, Denmark	First attack/recurrence	25–35
	USA, Finland	First attack/recurrence	70–80
Tinto et al.[3] (2002)	UK	First attack/recurrence	14.5–20.7
Andersson et al.[4] (2004)	Sweden	First attack/recurrence	30
Lankisch et al.[5] (2002)	Germany	First attack/recurrence	19.7
Gislason et al.[6] (2004)	Norway	First attack/recurrence	30.6
		First attack	20
Birgisson et al.[7] (2002)	Iceland	First attack	32
Floyd et al.[8] (2002)	Denmark	Men	27.1
		Women	37.8
Japan National Survey (1987)	Japan	First attack/recurrence	12.1
Japan National Survey (1998)	Japan	First attack/recurrence (Total)	15.4
		First attack/recurrence (men)	20.5
		First attack/recurrence (women)	10.6

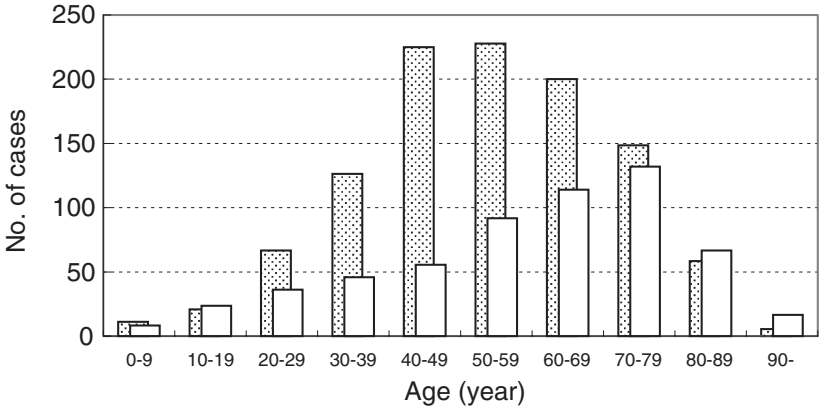

Fig. 1. Incidence of acute pancreatitis in Japan in 1998. Men, *shaded bars*; women, *white bars*

Table 2. Etiology and incidence of acute pancreatitis in Japan (national survey in 1999)

	All cases			Severe cases		
	Men (%)	Women (%)	Total (%)	Men (%)	Women (%)	Total (%)
Alcohol	466 (42)	42 (7.2)	508 (30)	138 (49)	14 (11)	152 (37)
Cholelithiasis	219 (20)	183 (31)	402 (24)	44 (16)	37 (30)	81 (20)
Abdominal injury	8 (0.7)	3 (0.5)	11 (0.7)	5 (1.8)	0 (0.0)	5 (1.2)
Surgery	25 (2.3)	18 (3.1)	43 (2.6)	4 (1.4)	3 (2.4)	7 (1.7)
ERCP	27 (2.5)	38 (6.5)	65 (3.9)	6 (2.1)	6 (4.8)	12 (2.9)
EST	12 (1.1)	16 (2.7)	28 (1.7)	5 (1.8)	8 (6.4)	13 (3.2)
Exacerbation of chronic pancreatitis	73 (6.6)	22 (3.7)	95 (5.6)	6 (2.1)	2 (1.6)	8 (2.0)
Pancreatic cancer	7 (0.6)	4 (0.7)	11 (0.7)	3 (1.1)	2 (1.6)	5 (1.2)
Pancreatobiliary maljunction	8 (0.7)	7 (1.2)	15 (0.9)	1 (0.4)	0 (0.0)	1 (0.2)
Pancreas divism	5 (0.5)	3 (0.5)	8 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Autoimmune diseases	0 (0.0)	4 (0.7)	4 (0.2)	0 (0.0)	1 (0.8)	1 (0.2)
Hyperlipidemia	10 (0.9)	10 (1.7)	20 (1.2)	4 (1.4)	3 (2.4)	7 (1.7)
Drugs	10 (0.9)	11 (1.9)	21 (1.2)	4 (1.4)	4 (3.2)	8 (2.0)
Idiopathic	186 (16.9)	196 (33)	392 (23)	51 (18)	38 (30)	89 (22)
TAE/TAI for hepatoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (18)	0 (0.0)	0 (0.0)
Others	42 (3.8)	30 (5.1)	72 (4.3)	12 (4.2)	7 (5.6)	19 (4.7)
Subtotal	1098 (100)	587 (100)	1685 (100)	283 (100)	125 (100)	408 (100)
Blank	0	3	3	0	1	1
Total	1098 (100)	590	1688	283	126	409

ERCP, endoscopic retrograde cholangiopancreatography; EST, endoscopic sphincterotomy; TAE, transcatheter arterial embolization; TAI, transcatheter arterial infusion

pancreatitis is considered to be associated with high levels of alcohol consumption.[18] In contrast, the incidence of gallstone pancreatitis is much higher than that of alcoholic pancreatitis in Greece, Italy, and Norway.[6,14] In France, Germany, and Korea, the incidence of acute alcoholic pancreatitis is slightly higher than that for gallstone pancreatitis,[14,16] whereas the opposite is true in Mexico and Sweden.[4,17] According to a 1999 national survey done in Japan (Table 3), the incidence of acute alcoholic pancreatitis was fairly similar to that of gallstone pancreatitis (30% vs. 24%). However, the survey classified as alcoholic pancreatitis those cases in which the consumption of only a small amount of alcohol was identified before the onset of symptoms, so the incidence of alcoholic pancreatitis may have been overestimated. Thus, it remains unknown whether alcoholic pancreatitis or gallstone pancreatitis has a higher incidence in Japan.

Sex is strongly associated with the risk of acute pancreatitis: the incidence of alcoholic pancreatitis is higher in men, and the incidence of gallstone pancreatitis is higher in women.[14,19] A study on acute pancreatitis in five European countries revealed that there were many more cases of alcoholic pancreatitis in men than women (90% vs. 10%).[14] The 1999 survey done in Japan[20] also revealed that in women the incidence of gallstone pan-

Table 3. Etiology of acute pancreatitis by country

Author (year)	Country	Alcohol (%)	Cholelithiasis (%)	Others (%)
Gullo et al.[14] (2002)	Hungary	60.7	24.0	15.3
	France	38.5	24.6	36.9
	Germany	37.9	34.9	27.2
	Greece	6.0	71.4	22.6
	Italy	13.2	60.3	26.5
Cavallini et al.[15] (2004)	Italy	8.5	60	31.5
Andersson et al.[4] (2004)	Sweden	30	35	35
Gislason[6] (2004)	Norway	17	47	36
Kim[16] (2003)	Korea	32.5	26.6	40.9
Suazo-Barahona et al.[17] (1998)	Mexico	34	43	23
National survey (1998)	Japan	30	24	46

creatitis was higher than that of alcoholic pancreatitis (31% vs. 7.2%), whereas in men the incidence of acute alcoholic pancreatitis was twice that of gallstone acute pancreatitis (42% vs. 20%). A similar tendency was observed for severe cases (Table 3). However, a German study showed that there was no gender difference in the risk of acute pancreatitis after adjusting for alcohol intake.[21]

Tamakoshi et al. conducted a case-control study to investigate risk factors associated with the onset of acute pancreatitis.[22] Consumption of more than 100 g of alcohol within 24 h before the onset was significantly associated with the risk of acute pancreatitis (odds ratio: 4.4, 95% CI: 1.3–15.5). Lower lipid intake was also associated with risk of acute pancreatitis; the risk was lower (odds ratio: 0.49) in the one-third of subjects with the highest lipid intake than in the one-third with the lowest lipid intake. Smoking and average sleep duration were not associated with increased risk of acute pancreatitis.

CQ3. What are the risk factors for developing acute pancreatitis?

Alcohol

Alcohol is one of the two major etiological factors responsible for acute pancreatitis and several studies have attempted to quantify the risk of acute alcoholic pancreatitis. According to a cohort study in Germany done between 1988 and 1995, the incidence of acute alcoholic pancreatitis among those with the highest alcohol intake (alcohol consumption ≧60 g/day) was 91.5/100 000 per year for men and 81.9/100 000 per year for women.[21] However, even in the highest-risk group, the risk of acute alcoholic pancreatitis during a 25-year period was only 2%–3%. These findings suggest that factors other than alcohol also contribute to the occurrence of acute alcoholic pancreatitis.[23]

Cholelithiasis

Cholelithiasis is another major etiological factor responsible for acute pancreatitis. According to a study done in the United States,[24] 89 (3.4%) of 2583 cholelithiasis patients developed pancreatitis during the follow-up period, and the relative risk (RR) for acute pancreatitis in the cholelithiasis patients was 14/35 for men and 12/25 for women. After adjusting for age and sex, the risk of acute pancreatitis among patients with gallstones was 6.3 to 14.8 per 1000 patient-years. However, the risk dramatically decreased after cholecystectomy to 1.9 per 1000 patient-years for men and 2.0 per 1000 patient-years for women. The RR was decreased to 1/8 in patients who underwent cholecystectomy, and recurrence developed in only 2 of the 58 patients after cholecystectomy (Level 2b).[24]

Diehl et al. investigated clinical factors associated with the risk of acute biliary pancreatitis. Multivariate analyses showed that acute pancreatitis was associated with a stone diameter of less than 5 mm (odds ratio, 4.51; $P = 0.007$) and with mulberry-shaped gallstones (odds ratio, 2.25; $P = 0.04$) (Level 2c).[25]

Endoscopic retrograde cholangiopancreatography/ endoscopic sphincterotomy

Acute pancreatitis is one of the major complications of endoscopic retrograde cholangiopancreatography (ERCP). According to reports from the United States and Europe, the incidence of acute pancreatitis after diagnostic ERCP ranged from 0.4% to 1.5% (Level 2c).[26–28] The incidence of complications resulting from endoscopic sphincterotomy (EST) and therapeutic ERCP was found to be higher than that resulting from diagnostic ERCP (Levels 2b);[29,30] the incidence of acute pancreatitis after EST and therapeutic ERCP ranged from 1.6% to 5.4%,[26,27,29–31] and the incidence of severe acute pancreatitis ranged from 0.4% to 0.7%.[28,32]

Masci et al. conducted a meta-analysis of 15 prospective clinical studies on complications resulting from ERCP[33] and identified risk factors for post-ERCP acute pancreatitis. The relative risk of developing post-ERCP acute pancreatitis for suspected sphincter of Oddi dysfunction was 4.09 (95% CI: 3.37–4.96; $P < 0.001$); for women 2.23 (95% CI: 1.75–2.84, $P < 0.001$); for patients with previous pancreatitis 2.46 (95% CI: 1.93–3.12, $P < 0.001$); for precut sphincterotomy 2.71 (95% CI: 2.02–3.63, $P < 0.001$); and for pancreatic injection 2.2 (95% CI: 1.6–3.01, $P < 0.001$). The following factors have also been enumerated as additional risk factors for acute pancreatitis: absence of cholangiectasis,[26] bile duct diameter of less than 1 cm,[31,34–36] older patients,[26,37] difficulty in cannulation,[31,38,39] and performance of pancreatography.[26,35,40–42] Maldonado et al. reported that the combined use of ERCP and Oddi manometry markedly increased the risk of acute pancreatitis.[43] The incidence of pancreatitis in patients who underwent sphincter of Oddi manometry alone was significantly lower than that in patients who underwent both manometry and ERCP (9.3% vs. 26.1%, $P < 0.026$). The addition of EST to ERCP, however, had no impact on the risk of post-ERCP acute pancreatitis.[43] There were no consistent findings regarding the association between the use of low-osmolar (nonionic) contrast media and the risk of post-ERCP acute pancreatitis, and the issue is still being debated (Levels 1b-2b).[29,30,44]

A few studies have investigated post-ERCP acute pancreatitis in Japan. In 1979, Nakajima et al. analyzed complications after therapeutic ERCP in 25 large medical institutions across Japan.[45] In that survey, EST was performed in 468 patients over a 5-year period; 9 (2%) of them developed pancreatitis, but none died. Another nationwide survey targeted 28 large medical institutions[46] and revealed that of the 14947 patients who underwent diagnostic or therapeutic ERCP between January 1995 and December 1998, 166 (1.1%) developed complications. Acute pancreatitis occurred in 89 (0.8%) of the patients who underwent diagnostic ERCP, and the incidence following therapeutic ERCP was 1.9%. The incidence of severe acute pancreatitis among the patients who underwent diagnostic ERCP and therapeutic ERCP was 0.07% and 0.1%, respectively. One patient who underwent therapeutic ERCP died, and the overall mortality was 0.007%. The mortality rate among patients who underwent therapeutic ERCP was 0.02%.

In the 1980s, there was a lawsuit brought in Japan after a patient treated by ERCP developed acute pancreatitis and died. In that case, the court decided that reparation had to be made for the loss. Since then, physicians involved in endoscopy and endoscopic treatment in Japan have striven to prevent acute pancreatitis, and the Japan Gastroenterological Endoscopy Society has developed guidelines to prevent complications related to endoscopy and endoscopic treatment.[47]

Surgery and medical procedures

The incidence of postoperative pancreatitis is high after surgery conducted near the pancreas, such as biliary tract procedures, gastric surgery, splenectomies, and splenorenal shunts (Level 4).[48,49] Before the introduction of ERCP and laparoscopic cholecystectomy, the risk of postoperative acute pancreatitis in patients undergoing biliary surgery was reported to be as high as 10%, with a mortality of 30%–80%.[50] Z'graggen et al. compared the incidence of postoperative pancreatitis after laparoscopic cholecystectomy (LC) and found that the risk of pancreatitis increased after conversion to an open cholecystectomy; the incidence of pancreatitis after completed LC was 0.34%, whereas that after conversion was 0.96% ($P = 0.02$).[51] It was possible to establish a biliary origin for the pancreatitis in 4 (12.5%) of the 32 patients with postoperative pancreatitis, and no evidence was found for a causative role of intraoperative cholangiography or trauma to the pancreas (Level 2c).[51]

There have been many reports of pancreatitis developing after cardiovascular surgery[52–57] or transplantation (e.g., pancreas, liver, kidney, heart, or bone marrow).[58–60] Ramsey and Podratz investigated the incidence of postoperative pancreatitis after gynecological and obstetric surgery and found that it was very low overall, occurring in only 1 of 17000 surgical procedures (Level 2c).[61]

Other reports have shown the occurrence of acute pancreatitis following extracorporeal shock wave lithotripsy (ESWL) for gallbladder stones (2%),[62] following transcatheter arterial embolization (TAE, 33%),[63] following percutaneous biliary drainage (PBD) (24% developed postprocedural hyperamylasemia and 10% developed postoperative acute pancreatitis),[64] following biliary stent insertion (11.5F stent, 3%; 10F stent, none),[65] following intraoperative irradiation (2/98, 2%),[66] and following continuous ambulatory peritoneal dialysis (CAPD) (0.46 per 100 treatment-years).[67] However, it remains unclear whether these procedures increase the risk of acute pancreatitis.[68]

Drugs

Many studies have suggested associations between the use of drugs and the risk of acute pancreatitis, but direct associations have been demonstrated for only a small number of drugs (Table 4).[69–80] The interval between drug administration and the onset of symptoms differs depending on the drug. Certain drugs, such as ace-

Table 4. Drugs that have been reported to cause acute pancreatitis

L-Asparaginase (anticancer drug)
Azathioprine (immunosuppressant)
Didanosine (anti-HIV drug)
Estrogen
Frosemide (diuretic)
Pentamidine (for pneumocystis carinii infection)
6-Mercaptopurine (anticancer drug)
Salicylates (antipyretic drug)
Stibogluconate sodium (antiprotozoal drug)
Sulfonamide (antimicrobial drug)
Sulindac (antipyretic drug)
Vincristine (anticancer drug)
Vinblastine (anticancer drug)

taminophen, can cause pancreatitis after a single dose. Others, such as azathioprine, 6-mercaptopurine, metronidazole, aminosalicylates, and sulfonamides, characteristically can cause pancreatitis within a month after exposure, while still others, such as pentamidine, valproic acid, and didanosine, appear to cause injury weeks or months after exposure, possibly through the accumulation of a toxic metabolite (Level 4).[80]

The drugs reported to be associated with the highest incidence of acute pancreatitis are azathioprine, mercaptopurine, and didanosine. An early study on the risk of acute pancreatitis associated with 6-mercaptopurine reported that 13 (3.3%) of 400 patients with inflammatory bowel disease developed acute pancreatitis.[81] However, a case-control study of 490 000 residents of Denmark[82] showed that the risk of acute pancreatitis in patients under treatment with azathioprine was only 1/659. In that study, the odds ratio for the risk of acute pancreatitis within 90 days after azathioprine administration was 7.5 (95% CI: 2.6–21.6), and after adjusting for cholelithiasis, alcohol, inflammatory intestinal diseases, and steroids, the odds ratio was 8.4 (95% CI: 2.6–21.6). Although many HIV patients treated with didanosine develop acute pancreatitis,[83–85] the independent risk associated with use of the drug is unknown (See HIV infection, below).

According to a case-control study done in Sweden over a 4-year period, 462 of the 1.4 million registered residents aged between 20 and 85 who did not have a clear etiological factor for their acute pancreatitis were hospitalized on their first attack of acute pancreatitis. A multivariate analysis revealed that H2 blockers, proton pump inhibitors, NSAIDs, and antacids were significantly associated with the risk of acute pancreatitis, but the odd ratios were generally low (1.9–2.4).[86]

Hyperlipidemia

High blood triglyceride levels of more than 1000–2000 mg/dl are said to increase the risk of acute pancreatitis.[87] Type V hyperlipidemia, as well as types I and IV, are prominent causes of acute pancreatitis as a result of marked hyperlipidemia (Level 4).[88] Secondary hyperlipidemia is caused by alcohol intake, pregnancy, estrogen therapy, and diabetes mellitus, all of which are risk factors for acute pancreatitis. Genetic polymorphism of lipoprotein lipase and the apolipoprotein C-II defect, which cause hyperlipidemia, are also suggested to cause acute pancreatitis (Level 4).[89,90] Some recent studies have suggested an association between the risk of acute pancreatitis and marked hypertriglyceridemia related to the administration of protease inhibitors among patients with HIV infection.[91,92] However, other reports argue that there is no association between the two.[87,93]

The risk of acute pancreatitis associated with hyperlipidemia has yet to be determined. A large-scale cohort study showed that hyperlipidemia accounts for 12%–38% of all cases of acute pancreatitis,[94] whereas another study suggested that it accounts for only 1.3%–3.8%.[95]

HIV infection

Acute pancreatitis is one of the main complications of acquired immunodeficiency syndrome (4%–22%), and the risk increases with the progression of HIV infection.[71] The risk of acute pancreatitis in HIV-infected populations is 35 to 800 times higher than in populations without infection.[83–85] Although HIV-infected patients may develop pancreatitis for many reasons, drugs are a common cause of acute pancreatitis. Before the introduction of antiretroviral therapy, the major mechanisms responsible for the development of acute pancreatitis among HIV-infected patients were: (1) pancreatic toxicity resulting from drugs used to treat HIV infection and (2) immunosuppression by the HIV infection itself.[87,96,97] Since 1996, when protease inhibitors were released on the market and came to be widely used in the treatment of HIV infection, HIV-infected patients have had a higher incidence of medication-associated hypertriglyceridemia, which is often severe and difficult to treat, and several reports have suggested that hypertriglyceridemia may be involved in the onset of acute pancreatitis.[91,92]

Bush and Kosmiski investigated whether the release of protease inhibitors onto the market changed the incidence of acute hyperlipidemic pancreatitis in HIV-infected patients.[87] Despite the well-established association between protease inhibitors and hyperlipidemia, there was no significant increase in the prevalence of hyperlipidemic patients in the HIV-infected population: the incidence of acute pancreatitis attributed to hypertriglyceridemia (serum neutral fat level $\geqq$1000 mg/dl) was 3.3% before the sale of protease inhibitors (1990–1995) and 3.7% after they came on the

market (1996–2001) ($P = 0.6$). On the other hand, medication-induced pancreatitis was the most common kind in HIV-infected patients: the incidence of medication-induced acute pancreatitis was 46.6% before the release of protease inhibitors and 50.0% after the release ($P = 0.6$).

Idiopathic

After gallstones and alcohol, the third most common etiology of acute pancreatitis, regardless of country, region, or case series, is idiopathic. Acute idiopathic pancreatitis is defined as acute pancreatitis with a nonspecified etiological factor, but it includes those cases caused by other specific disorders. Two prospective studies of apparently idiopathic pancreatitis have found that two-thirds to three-quarters of the cases had microlithiasis documented by biliary-drainage studies, follow-up sonograms, and ERCP (Level 2b).[98,99] In the treatment of acute pancreatitis, the diagnosis of acute idiopathic pancreatitis should be minimized by identifying the etiological factors based on clinical symptoms and findings as well as appropriate tests.

Other factors associated with acute pancreatitis

Other factors associated with acute pancreatitis are inherited conditions,[94,96] pregnancy,[100–102] trauma,[103,104] viral infections (mumps, Coxsackie B, hepatitis B, cytomegalovirus, herpes simplex II, and varicella-zoster), bacterial infections (*Salmonella typhi*, *Leptospira*, and *Legionella*), fungal infection (*Aspergillus*), parasites (*Toxoplasma*, *Cryptosporidium*, *Ascaris lumbricoides*, and *Mycoplasma*[105]), collagen diseases (including systemic lupus erythematosus,[106–108] rheumatoid arthritis,[109] Sjogren's syndrome,[110] and systemic sclerosis[111–112]), hyperparathyroidism,[113–116] and end-stage renal failure.[117,118]

Many studies have suggested the involvement of local predisposing anatomic factors in the etiology of acute pancreatitis. The presence and diameter of a common channel, pancreatic duct reflux, the angle formed between the common bile duct and the pancreatic duct, abnormalities of the Vater's ampulla (edema, hemorrhage, and impacted calculi), patent Santorini's duct, and the position of confluence with the cystic duct have all been suggested to be associated with the development of acute pancreatitis (Levels 2b–3b).[119–122] Pancreas divisum, a congenital variant of pancreatic ductal anatomy that affects 5%–7% of the general population, has also been suggested to be associated with acute pancreatitis. Some reports have shown a significantly higher incidence of pancreas divisum among patients with acute pancreatitis, including recurrent pancreatitis (Levels 3b–4).[123,124] However, another study reported no difference in any of these parameters between acute pancreatitis patients and healthy subjects (Level 2b).[125] A randomized controlled clinical trial showed that stenting of the accessory papilla interrupted the cycle of recurrent attacks of pancreatitis in patients with pancreas divisum (Level 1b).[126] Associations between acute pancreatitis and choledochocele (choledochal cyst),[127,128] peripapillary diverticulum,[129] ectopic pancreas,[130] pancreatitis caused by duodenal duplication,[131] pancreatitis accompanying Caroli's disease,[132] and pancreatitis caused by tumors of the pancreas (cancer of the pancreas,[133–135] metastatic pancreatic tumors,[136] and carcinoid tumors[137]) have also been reported (Level 4). However, it remains unclear whether the incidence of acute pancreatitis is higher in these patients than in healthy subjects.

Acute pancreatitis in childhood is unusual, and the etiology in children differs from the etiology in adults. Steinberg and Tenner reviewed 5 studies involving a total of 223 children with acute pancreatitis[80] and reported that trauma is the leading cause of acute pancreatitis in children, accounting for 21% of the cases, followed by idiopathic causes (20%), biliary tract disease (17%), drugs (15%), infections (10%), congenital anomalies (6%), and miscellaneous causes (11%).

CQ4. What are the outcomes of acute pancreatitis?

Recurrence of acute pancreatitis

The rate of recurrence of acute pancreatitis is relatively high, although it depends on etiological factors and interventions in response to those factors. A study of 1376 inpatients with acute pancreatitis (2211 episodes) during the 22-year period from 1975 to 1996 at a university hospital in Sweden revealed that 21% had had a recurrence and that two-thirds of them had experienced the recurrence within 3 months of the first attack.[4] According to a prospective cohort study on the recurrence of acute alcoholic pancreatitis,[138] 46% had a recurrence of the disease, and 80% of the recurrent episodes developed within 4 years of the first attack. The recurrence rate did not change over time (Level 1b). Several studies have reported that the risk of recurrence of gallstone pancreatitis ranges from 32% to 61% when the gallstones are not treated at the initial hospitalization.[139–141] On the other hand, another report has shown that idiopathic pancreatitis recurred on average in 1 of 31 patients during the subsequent 3 years (Level 1b).[142] Lee et al. prospectively studied 23 patients who were diagnosed with idiopathic acute pancreatitis but had microscopic evidence of biliary sludge, and they found that the 12 patients who were treated by cholecystectomy or papillotomy had fewer recurrences than the 11 untreated patients ($P = 0.01$) (Level 1b).[99]

In Japan, a study group on acute pancreatitis conducted a follow-up survey of 204 patients with severe acute pancreatitis who survived to discharge (excluding 27 late deaths) between 1982 and 1987.[143] The results of the survey showed that the overall recurrence rate for acute pancreatitis over the long term was 37%. Forty-eight percent of the patients received treatment for recurrent acute pancreatitis, as well as for complications such as diabetes mellitus and pancreatic pseudocyst, and 56% of those cases required hospitalization. The recurrence rates differed between various etiologies. The recurrence rate in patients with alcoholic pancreatitis was 51%, which was significantly higher than that among those with other etiological factors (Level 2b).[143] Whereas 67% of patients with alcoholic pancreatitis received medical treatment, only 29% of those with gallstone pancreatitis required medical treatment. However, the following must be taken into consideration when interpreting this survey: (1) the subjects were restricted to severe cases, (2) some cases with a favorable course may not have been included in the survey, and (3) some cases of chronic pancreatitis may have been classified as recurrent cases.

Development of chronic pancreatitis

The incidence of chronic pancreatitis after acute pancreatitis ranges from 3% to 13% (Levels 2b–4).[144,145] Angelini et al. investigated the frequency of residual ductal lesions in 118 patients who had recovered from acute pancreatitis. Occlusive pancreatitis was identified by ERCP in 7 patients (8.4%) who had recovered from necrotizing pancreatitis, and calcified pancreatitis was observed in 3 such patients (3.6%). Both percentages were higher than they were for those patients who had recovered from edematous pancreatitis (Level 1b).[146] A nationwide survey on the long-term outcome in severe pancreatitis patients in Japan revealed that pancreatic calculi were subsequently identified in 17% of such patients (33.5% of the alcoholic pancreatitis patients and 6.5% of the gallstone pancreatitis patients) and glucosuria was identified in 27% (40% of the alcoholic pancreatitis patients and 14% of the gallstone pancreatitis patients) (Level 2b).[146] These data suggest that the severity of, and the etiological factors for, pancreatitis are closely associated with the development of chronic pancreatitis.

Mortality

Many cases of acute pancreatitis are first diagnosed at autopsy. Reports in the 1980s (Levels 2b–4)[147,148] showed that the diagnosis was made at necropsy in about 30%–40% of fatal cases of acute pancreatitis. Recent reports have also shown that the diagnosis of acute pancreatitis was made at necropsy in 12%–33% of fatal cases.[149,150]

The case fatality of acute pancreatitis depends on the diagnostic criteria, as well as on whether autopsied cases are included.[151] Studies published after 1990 have shown that the case fatality of acute pancreatitis in the United States and Europe ranges from 2.1% to 7.8% (Levels 1b–2b) (Table 5).[147,149,151] Many studies have suggested that age is the primary risk factor for death

Table 5. Mortality from acute pancreatitis

Author	Study period	Setting/ country	All cases	Deaths	Mortality (%)
Andersson et al.[4]	1975–1985	University hospital, Sweden			4.7
	1986–1996	University hospital, Sweden			3.7
Mann et al.[149]	1988–1992	Northwest Thames region, UK	631	57	9.0
Talamini et al.[152]	1976–1992	University hospital, Italy	192[a]	17	8.8
Lowham et al.[153]	1996–1997	Infirmary, England	105	6	5.7
Mutinga et al.[154]	1982–1995	Large tertiary care hospital, USA	805	17	2.1
Blum et al.[155]	1988–1999	Luneburg County, Germany	351	17	4.6
Floyd et al.[8]	1981–1985	Denmark	480	44	9.2
	1986–1990	Denmark	475	40	8.4
	1991–1995	Denmark	609	40	6.6
	1996–2000	Denmark	786	53	6.7
Lankisch et al.[5]	1988–1995	Germany	228	16	7.0
Gullo et al.[14]	1990–1994	Hungary, Germany, France, Italy, Greece	1068	83	7.8
Kim[16]	1980–1989	Korea			3.0
	1990–1994	Korea			4.4
	1995–1999	Korea			2.1
Kandasami et al.[156]	1994–1999	Malaysia	133		7.5
National survey[157]	1995–1998	Japan	1240	92	7.4

[a] First attack cases only

(Level 1b).[150,151] A Japanese survey done from 1991 to 1995 showed that the mortality of severe acute pancreatitis is greater than 20% in patients over 50 years of age (Level 1b).[158] According to a 1988 nationwide survey done in Japan,[12] acute pancreatitis mortality was 2% in moderate cases and 30% in severe cases (Level 4). According to a 1999 nationwide surveillance,[20] overall mortality was 7.4% and 22% in the severe cases in Japan (Level 4).

There is a debate as to whether the mortality of acute pancreatitis has been decreasing in recent years. A few studies have suggested that the in-hospital mortality is declining. Andersson et al. reported that the hospital mortality of acute pancreatitis in a university hospital in Sweden decreased slightly, from 4.7% (1975–1985) to 3.7% (1986–96), and that the average age of the patients who died markedly increased, from 59.2 to 73.6 years of age.[4] Tinto et al. have also shown a significant decline in the hospital mortality rate for acute pancreatitis between the periods 1989–1990 and 1999–2000, during which the age standardized hospital admission rate for acute pancreatitis increased by 43%.[3] We must be careful in interpreting such data, because the level of patient risk and the patient background may be different between the study periods.

Mortality among patients with recurrent attacks is generally lower than among those experiencing their first attack. A study of 737 hospitalized patients with acute pancreatitis in Bristol, England, revealed that the overall mortality between 1968 and 1979 was 20%, but it was 12% in the patients with recurrent pancreatitis (Level 4).[159] Another hospital-based study showed that the mortality of patients with relapsing attacks (2.5%) was significantly lower than the overall mortality (4.2%) among acute pancreatitis patients.[4] A European study of acute pancreatitis that selected 1068 patients in 5 countries (Hungary, Germany, Greece, Italy, and France) also showed significantly lower mortality in recurrent pancreatitis than was the overall mortality from acute pancreatitis (5.9% vs. 7.8%).[14,152]

Factors associated with prognosis

The prognosis of acute pancreatitis is determined by two factors that reflect the severity of the disease: organ failure and pancreatic necrosis. Pancreatic necrosis can be evaluated by dynamic contrast-enhanced computed tomography (CT) scanning.[160,161] According to the definitions of the 1992 Atlanta Symposium, the criteria for organ failure include the following parameters: (1) shock — systolic blood pressure <90 mmHg, (2) respiratory failure — PaO_2 <60 mmHg, (3) renal failure — serum creatinine >2 mg/dl after hydration, and (4) gastrointestinal bleeding — blood loss >500 ml/24 h. The Research Group sponcered by JMHW has established independent criteria for the assessment of the severity,[162] and the parameters include dyspnea; shock; central nervous system disorders; bleeding tendency; negative base excess; and signs of organ failure, including elevation of the blood urea nitrogen level and the creatinine level.

Timing of death in acute pancreatitis

Many acute pancreatitis patients die within the first few weeks of the onset of the illness. According to reports published since 2000, about half of the deaths occur within the first 1–2 weeks, and they are mainly the result of multiple organ dysfunction syndrome (MODS)[154,155] (Table 6). In general, late mortality in patients with severe acute pancreatitis results mainly from complications caused by infection, particularly by infectious pan-

Table 6. Comparison of mortality and time of death in acute pancreatitis [National Survey Data (Japan) added to data from the review by Blum et al.]

Author	Number of cases	Overall mortality		Proportion of early deaths (%)		Proportion of late deaths (%)	
		n	%	*n*	%	*n*	%
Mann et al.[149]	631	57	9	18	32[a]	39	68
Talamini et al.[152]	192	17	9	14	82[b]	3	18
Lowham et al.[153]	105	6	6	6	100[a]	—	—
McKay et al.[151]	NA	NA	8	NA	54[a]	—[c]	46
Mutinga et al.[154]	805	8	2	8	47[b]	9	53
Blum et al.[155]	368	17	5	7	41[a]	10	59
National Survey	1131	67[d]	6	19	28[a]	48	72
(Japan)[157]	1131	67[d]	6	27	40[b]	40	60

[a] Early mortality was defined as death within 1 week
[b] Early mortality was defined as death within 2 weeks
[c] No single piece of data given
[d] Includes only the 67 cases in which acute pancreatitis was presumed to be the cause of death among a total of 94 fatal cases

Table 7. Mortality from acute necrotizing pancreatitis

Author (year)	Acute pancreatitis, all causes		Severe acute pancreatitis		Necrotizing acute pancreatitis	
	n	Mortality (%)	*n*	Mortality (%)	*n*	Mortality (%)
Karimgani et al.[173] (1992)			26[a]	38		
Bradley and Allen[174] (1991)	194				38	15
Rattner et al.[175] (1992)					73	25
Allardyce[172] (1987)	348	5.2	43	33	17	80
Perez et al.[170] (2002)	1110				99	14
Gullo et al.[14] (2002)	1068	7.8			479	16
Lankisch et al.[176] (2002)	326	7.1			64	
Japan's national survey[177] (2000)	1240	7.4	409	22	117	23

[a] Patients with at least one systemic complication

creatic necrosis (Levels 2c–4).[163–165] Gloor et al. have argued that early mortality associated with acute pancreatitis has decreased as a result of modern intensive care treatment.[166] In their case series, the overall mortality rate was 4% and the mortality rate in patients with necrotizing pancreatitis was 9%. On the other hand, some argue that many patients with acute pancreatitis still die within the first 1–2 weeks after admission.[167] In a large study of acute pancreatitis in the United Kingdom, 35 deaths occurred among 283 patients with severe acute pancreatitis, and 13 of those occurred within the first week of illness.[168] Japanese surveys define early mortality as death within 2 weeks of admission, and the early mortality rate was 52% in the period 1982–1986; it then markedly decreased to 29% in 1996.[169] According to a 1988 survey, shock followed by severe dehydration was the leading cause of early death, and the cause of those deaths that occurred after 2 weeks included renal failure, respiratory failure, gastrointestinal hemorrhage, sepsis, and shock (Level 2c).[12,13] According to a 1999 survey,[157] acute pancreatitis was the direct cause of death in 67 (73%) of 92 cases. Twenty-seven deaths (40%) occurred within 2 weeks of onset, and MODS accounted for 85.2% of these. Another 40 deaths occurred 2 weeks or more after onset, and MODS, including sepsis (67.5%) and disseminated intravascular coagulation syndrome (62.5%), accounted for as many as 87.5% of those deaths.

Necrotizing pancreatitis

Depending on patient selection, necrotizing pancreatitis develops in approximately 10%–20% of acute pancreatitis patients, and mortality is high; however, mortality is only 1%–3% among those without necrotizing pancreatitis.[14,170,171] A report from the 1980s indicated a mortality of 80% among patients with necrotizing pancreatitis,[172] whereas figures from the 1990s have ranged from 14% to 25% (Table 7). According to a Japanese survey done in 1999,[20] 409 (33%) of the patients developed a severe disease. Contrast-enhanced CT scanning was performed in 75% of these patients, and pancreatic necrosis was observed in 42% of them. Based on these findings, the incidence of pancreatic necrosis in Japan is estimated to be 10%–15% (Level 3b). In this survey, the mortality of severe acute pancreatitis with pancreatic necrosis was 23%, whereas the mortality in severe acute pancreatitis without pancreatic necrosis was 11%.

It has been suggested that the outcome of necrotizing pancreatitis is associated with the extent of necrosis and infectious complications (Level 4).[169,178] Perez et al. classified 99 patients with necrotizing pancreatitis into two groups according to the extent of necrosis (<50% or ≧50%); they compared outcomes between the two groups but found no significant difference in the Acute Physiology and Chronic Health Evaluation (APACHE) II scores, the incidence of infected necrosis, MODS, or organ failure. MODS and organ failure were strongly associated with death. When organ failure accompanied necrotizing pancreatitis, mortality increased to 47%; mortality among the patients with MODS was 49%.[170]

According to reports from the United States and Europe, infected pancreatic necrosis develops in 30%–40% of patients with necrotizing pancreatitis.[170] A 1999 survey done in Japan revealed that infected pancreatic necrosis occurred in 152 (41%) of the 367 patients (42 patients with unconfirmed infection were excluded from 409 severe acute pancreatitis patients), and mortality was 34% in infected pancreatic necrosis, as opposed to only 7% in pancreatic necrosis without infection. According to the report by Perez et al., the mortality in infected necrosis was 19% (7/37), as opposed to only 11% (7/62) in sterile necrosis. Although the difference in mortality between these groups was not statistically significant, the incidence of multiple organ failure, which strongly affects the outcome, was much higher in

the infected necrosis patients than in the sterile necrosis patients (41% vs. 23%, $P = 0.07$). It cannot be denied that necrotizing pancreatitis is strongly linked to the outcome.

Long-term outcome

About one-third to one-half of acute pancreatitis patients develop functional disorders of both the endocrine system and the exocrine system (diabetes mellitus and fatty stool). However, many reports have shown that most patients are in good general health at the time of discharge and return to their usual daily routine (Level 4).[156,179,180] Although the age-standardized mortality rate of patients who recovered from acute pancreatitis is higher than those without the disease, the mortality was no different among patients over 65 years of age (Level 4).[143] Symptoms tend to decrease with time among patients with fatty stool, whereas the symptoms of diabetes mellitus deteriorate (Level 1b).[181] On the other hand, some authors have emphasized that endocrine function disorders after severe acute pancreatitis are associated with pancreatic resection (Level 2b),[182] since insulin secretion is significantly decreased after pancreatic resection compared with conservative treatments such as peritoneal lavage.

In 1999, a survey was done by the Japanese Ministry of Health, Labour and Welfare that targeted 2098 patients who had experienced severe acute pancreatitis in 1987.[183] Information was gathered on 714 (34%) of those patients. Some 15% had died, 22% had experienced a recurrence, 24% had progressed to chronic pancreatitis, and 13% had developed diabetes mellitus. Some 80% of the respondents had been able to return to their usual daily routine, i.e., the same routine that they had enjoyed before the onset of the disease. The most frequent cause of death was a malignant tumor (36%). Forty-six percent of the patients who had a recurrence experienced it within 1 year of the initial attack.[183]

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