

Definitions, pathophysiology, and epidemiology of acute cholangitis and cholecystitis: Tokyo Guidelines

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Abstract

This article discusses the definitions, pathophysiology, and epidemiology of acute cholangitis and cholecystitis. Acute cholangitis and cholecystitis mostly originate from stones in the bile ducts and gallbladder. Acute cholecystitis also has other causes, such as ischemia; chemicals that enter biliary secretions; motility disorders associated with drugs; infections with microorganisms, protozoa, and parasites; collagen disease; and allergic reactions. Acute acalculous cholecystitis is associated with a recent operation, trauma, burns, multisystem organ failure, and parenteral nutrition. Factors associated with the onset of cholelithiasis include obesity, age, and drugs such as oral contraceptives. The reported mortality of less than 10% for acute cholecystitis gives an impression that it is not a fatal disease, except for the elderly and/or patients with acalculous disease. However, there are reports of high mortality for cholangitis, although the mortality differs greatly depending on the year of the report and the severity of the disease. Even reports published in and after the 1980s indicate high mortality, ranging from 10% to 30% in the patients, with multiorgan failure as a major cause of death. Because many of the reports on acute cholecystitis and cholangitis use different standards, comparisons are difficult. Variations in treatment and risk factors influencing the mortality rates indicate the necessity for standardized diagnostic, treatment, and severity assessment criteria.

Key words Gallstones · Biliary · Bile · Biliary infection · Cholangitis · Acute cholecystitis · Guidelines

Introduction

Acute biliary infection is a systemic infectious disease which requires prompt treatment and has a significant mortality rate.¹ The first report on acute biliary infection was Charcot's "The symptoms of hepatic fever" in 1877.²

This section of the Tokyo Guidelines defines acute cholangitis and acute cholecystitis, and describes the incidence, etiology, pathophysiology, classification, and prognosis of these diseases.

Acute cholangitis

Definition

Acute cholangitis is a morbid condition with acute inflammation and infection in the bile duct.

Historical aspects of terminology

Hepatic fever. "Hepatic fever" was a term used for the first time by Charcot,² in his report published in 1877. Intermittent fever accompanied by chills, right upper quadrant pain, and jaundice became known as Charcot's triad.

Offprint requests to: Y. Kimura

Received: May 31, 2006 / Accepted: August 6, 2006

Acute obstructive cholangitis. Acute obstructive cholangitis was defined by Reynolds and Dargan³ in 1959 as a syndrome consisting of lethargy or mental confusion and shock, as well as fever, jaundice, and abdominal pain, caused by biliary obstruction. They indicated that emergent surgical biliary decompression was the only effective procedure for treating the disease. These five symptoms were then called Reynolds's pentad.

*Longmire's classification.*⁴ Longmire classified patients with the three characteristics of intermittent fever accompanied by chills and shivering, right upper quadrant pain, and jaundice as having acute suppurative cholangitis. Patients with lethargy or mental confusion and shock, along with the triad, were classified as having acute obstructive suppurative cholangitis (AOSC). He also reported that the latter corresponded to the morbidity of acute obstructive cholangitis as defined by Reynolds and Dargan,³ and he classified acute microbial cholangitis as follows:

1. Acute cholangitis developing from acute cholecystitis
2. Acute non-suppurative cholangitis
3. Acute suppurative cholangitis
4. Acute obstructive suppurative cholangitis
5. Acute suppurative cholangitis accompanied by hepatic abscess.

Incidence

Etiology

Acute cholangitis requires the presence of two factors: (1) biliary obstruction and (2) bacterial growth in bile (bile infection). Frequent causes of biliary obstruction are choledocholithiasis, benign biliary stenosis, stricture of a biliary anastomosis, and stenosis caused by malignant disease (level 4).^{5,6} Choledocholithiasis used to be

the most frequent cause of the obstruction, but recently, the incidence of acute cholangitis caused by malignant disease, sclerosing cholangitis, and non-surgical instrumentation of the biliary tract has been increasing. It is reported that malignant disease accounts for about 10%–30% of cases of acute cholangitis. Tables 1 and 2 show some results of studies on the causes of acute cholangitis.

Risk factors. The bile of healthy subjects is generally aseptic. However, bile culture is positive for microorganisms in 16% of patients undergoing a non-biliary operation, in 72% of acute cholangitis patients, in 44% of chronic cholangitis patients, and in 50% of those with biliary obstruction (level 4).¹² Bacteria in bile are identified in 90% of patients with choledocholithiasis accompanied by jaundice (level 4).¹³ Patients with incomplete

Table 1. Etiology of acute cholangitis

Cholelithiasis
Benign biliary stricture
Congenital factors
Postoperative factors (damaged bile duct, strictured choledojejunostomy, etc.)
Inflammatory factors (oriental cholangitis, etc.)
Malignant occlusion
Bile duct tumor
Gallbladder tumor
Ampullary tumor
Pancreatic tumor
Duodenal tumor
Pancreatitis
Entry of parasites into the bile ducts
External pressure
Fibrosis of the papilla
Duodenal diverticulum
Blood clot
Sump syndrome after biliary enteric anastomosis
Iatrogenic factors

Table 2. Causes of acute cholangitis (%)

Author	Year	Setting	N	Causes				
				GB stones	Benign stenosis	Malignant stenosis	Sclerosing cholangitis	Others/unknown
Gigot ⁶	1963–1983	University of Paris	412	48%	28%	11%	1.5%	—
Saharia and Cameron ⁷	1952–1974	Johns Hopkins Hospital, USA	76	70%	13%	17%	0%	—
Pitt and Couse ⁸	1976–1978	Johns Hopkins Hospital, USA	40	70%	18%	10%	3%	—
Pitt and Couse ⁸	1983–1985	Johns Hopkins Hospital, USA	48	32%	14%	30%	24%	—
Thompson ⁹	1986–1989	Johns Hopkins Hospital, USA	96	28%	12%	57%	3%	—
Basoli ¹⁰	1960–1985	University of Rome	80	69%	16%	13%	0%	4%
Daida ¹¹	1979	Questionnaire throughout Japan	472	56%	5%	36%	—	3%

obstruction of the bile duct present a higher positive bile culture rate than those with complete obstruction of the bile duct. Risk factors for bactobilia include various factors, as described above.¹⁴

Post-endoscopic retrograde cholangiopancreatography (ERCP) infectious complications. The incidence of complications after ERCP ranges from 0.8% to 12.1%, though it differs depending on the year of the report and the definition of complications (level 4).^{15–23} Overall post-ERCP mortality is reported to be between 0.5% and 1.5% (level 4).¹⁸ The most frequent complication is acute pancreatitis, but it is usually mild or moderate. Table 3 shows the reported incidence of various post-ERCP complications.

The incidences of post-ERCP acute cholangitis and cholecystitis are, as shown in Table 3, 0.5%–1.7% and 0.2%–0.5%, respectively.^{15–19} The complications caused by ERCP performed for diagnostic and for therapeutic purposes are different. Therapeutic ERCP tends to cause all complications, including cholangitis, more frequently than diagnostic ERCP.^{17,20}

The increasing use of ERCP and the improved operators' skills and techniques in recent years have reduced the incidence of post-ERCP complications, although the incidence of acute cholecystitis has not dropped and seems unpredictable.¹⁷

Other etiologies of acute cholangitis. There are two other etiologies of acute cholangitis; Mirizzi syndrome and Lemmel syndrome. Mirizzi syndrome is a morbid condition with stenosis of the common bile duct caused by mechanical pressure and/or inflammatory changes caused by the presence of stones in the gallbladder neck and cystic ducts.²⁴ Two types have been described: *type I*, which is a morbid condition with the bile duct compressed from the left by the presence of stones in the gallbladder neck and cystic ducts and pericholecystic inflammatory changes; and *type II*, which is a morbid condition with biliobiliary fistulation caused by pressure necrosis of the bile duct due to cholelithiasis.

Lemmel syndrome is a series of morbid conditions in which the duodenal parapapillary diverticulum compresses or displaces the opening of the bile duct or pancreatic duct and obstructs the passage of bile in the bile duct or hepatic duct, thereby causing cholestasis, jaundice, gallstone, cholangitis, and pancreatitis.²⁵

Pathophysiology

The onset of acute cholangitis involves two factors: (i) increased bacteria in the bile duct, and (ii) elevated intraductal pressure in the bile duct that allows translocation of bacteria or endotoxins into the vascular system (cholangio-venous reflux). Because of its anatomical characteristics, the biliary system is likely to be affected by elevated intraductal pressure. In acute cholangitis,

with the elevated intraductal biliary pressure, the bile ductules tend to become more permeable to the translocation of bacteria and toxins. This process results in serious infections that can be fatal, such as hepatic abscess and sepsis.

Prognosis

Patients who show early signs of multiple organ failure (renal failure, disseminated intravascular coagulation [DIC], alterations in the level of consciousness, and shock) as well as evidence of acute cholangitis (fever accompanied by chills and shivering, jaundice, and abdominal pain), and who do not respond to conservative treatment, should receive systemic antibiotics and undergo emergent biliary drainage.¹ We have to keep in mind that unless early and appropriate biliary drainage is performed and systemic antibiotics are administered, death will occur.

The reported mortality of acute cholangitis varies from 2.5% to 65%^{26–37} (Table 4). The mortality rate before 1980 was 50%,^{26,27} and after 1980 it was 10%–30%.^{28–37} Such differences in mortality are probably attributable to differences in early diagnosis and improved supportive treatment.

The major cause of death in acute cholangitis is multiple organ failure with irreversible shock, and mortality rates have not significantly improved over the years.^{26–33} Causes of death in patients who survive the acute stage of cholangitis include multiple organ failure, heart failure, and pneumonia.³⁴

Acute cholecystitis

Definition

Acute cholecystitis is an acute inflammatory disease of the gallbladder. It is often attributable to gallstones, but many factors, such as ischemia; motility disorders; direct chemical injury; infections with microorganisms, protozoa, and parasites; collagen disease; and allergic reaction are involved.

Incidence

Acute cholecystitis cases account for 3%–10% of all patients with abdominal pain.^{38–40} The percentage of acute cholecystitis cases in patients under 50 years old with abdominal pain ($n = 6317$) was low, at 6.3%, whereas that in patients aged 50 and over ($n = 2406$) was high, at 20.9% (average, 10%)⁴⁰ (Table 5).

Etiology

Cholelithiasis accounts for 90%–95% of all causes of acute cholecystitis, while acalculous cholecystitis accounts for the remaining 5%–10% (level 4).^{41–47}

Table 3. Reports of complications caused by ERCP

Author	Year of report	Type of ERCP	No. of cases	Total	Acute pancreatitis (all)	Acute pancreatitis (severe)	Acute cholecystitis	Acute cholangitis	Pain	Fever
Vandervoort ¹⁵	2002	Diagnostic, therapeutic ERCP	1223	11.2%	7.2%	0.5%	0.25%	0.7%	0.3%	1.6%
Freeman ¹⁶	1996	ERCP + EST	2347	9.8%	5.4%	0.4%	0.5%	1.0%		
Lenriot ¹⁷	1993	Diagnostic ERCP	407	3.6% (0.96%)	1.5% (0.2%)			1.5% (0.5%)		
Lenriot ¹⁷	1993	ERCP + EST	257	12.1% (3.9%)	1.6% (0.7%)			5.4% (0.8%)		
Benchimol ¹⁸	1992	Diagnostic, therapeutic ERCP	3226	0.9% (0.2%)	0.1%		0.2%	0.5%		
Cotton ¹⁹	1991	ERCP + EST	7729		1.9%			1.7%		
Reiertsen ²⁰	1987	Diagnostic ERCP	7314	0.18% (0.04%)						
Reiertsen ²⁰	1987	Therapeutic ERCP	1930	0.85% (0.05%)						
Roszler ²¹	1985		140	—	12.8%	—	—	—	—	—
Escourrou ²²	1984	EST	407	7% (1.5%)						
Bilbao ²³	1976		10435	3% (0.2%)						

Figures in parentheses denote mortality

Table 4. Mortality of acute cholangitis

Author	Period	Country	No. of subjects	Mortality (%)
Andrew ²⁶	1957–1967	USA	17 ^c	64.71
Shimada ²⁷	1975–1981	Japan	42 ^b	57.1
Csendes ²⁸	1980–1988	Chile	512	11.91
Himal and Lindsac ²⁹	1980–1989	Canada	61	18.03
Chijiwa ³⁰	1980–1993	Japan	27 ^c	11.11
Liu ³¹	1982–1987	Taiwan	47 ^a	27.66
Lai ³²	1984–1988	Hong Kong	86 ^b	19.77
Thompson ³³	1984–1988	USA	127	3.94
Arima ³⁴	1984–1992	Japan	163	2.45
Kunisaki ³⁵	1984–1994	Japan	82	10.98
Tai ³⁶	1986–1987	Taiwan	225	6.67
Thompson ³⁷	1986–1989	USA	96	5.21

^aOnly patients with shock^bOnly severe cases^cOnly AOSC**Table 5.** Acute cholecystitis in patients with abdominal pain

Reports of all patients with abdominal pain							
				Telfer ⁴⁰			
Eskelinen et al. ³⁸ <i>n</i> = 1333	Brewer et al. ³⁹ <i>n</i> = 1000		Under 50 years old (<i>n</i> = 6317)		50 years and over (<i>n</i> = 2406)		
Nonspecific abdominal pain	618	Unknown cause	413	Nonspecific abdominal pain	39.5%	Acute cholecystitis	20.9%
Appendicitis	271	Gastroenteritis	69	Appendicitis	32.0%	Nonspecific abdominal pain	15.7%
Acute cholecystitis	124	Intrapelvic infection	67	Acute cholecystitis	6.3%	Appendicitis	15.2%
Ileus	53	Urinary tract infection	52	Ileus	2.5%	Ileus	12.3%
Dyspepsia	50	Ureterolith	43	Acute hepatitis	1.6%	Acute hepatitis	7.3%
Ureterolith	57	Appendicitis	43	Diverticulitis	<0.1%	Diverticulitis	5.5%
Diverticulitis	19	Acute cholecystitis	25	Cancer	<0.1%	Cancer	4.1%
Mesenteric lymphadenitis	11	Ileus	25	Hernia	<0.1%	Hernia	3.1%
Acute pancreatitis	22	Constipation	23	Vascular lesion	<0.1%	Vascular lesion	2.3%
Peptic ulcer perforation	9	Duodenal ulcer	20				
Urinary tract infection	22	Dysmenorrhea	18				
Gynecological diseases	15	Pregnancy	18				
Others	62	Pyelitis	17				
		Gastritis	14				
		Chronic cholecystitis	12				
		Ovarian abscess	10				
		Dyspepsia	10				

Risk factors. Acute cholecystitis is the most frequent complication occurring in patients with cholelithiasis. According to the Comprehensive Survey of Living Conditions of the People on Health and Welfare conducted by the Medical Statistics Bureau of the Japanese Ministry of Health and Welfare, the number of those with

acute cholecystitis has increased, from 3.9 million in 1979 to over 10 million in 1993 (Public Welfare Index in Japan; 1933; level 4).

According to the review by Friedman,⁴⁸ of the natural history of cholelithiasis, serious symptoms or complications (acute cholecystitis, acute cholangitis, clinical

jaundice, and pancreatitis) were observed in 1%–2% of asymptomatic patients and in 1%–3% of patients with mild symptoms per year (Table 6), and the risk of complications increased in the first several years after the discovery of gallbladder stones, but then decreased (level 2c). Every year, 6%–8% of patients whose symptoms progress from minor to serious undergo cholecystectomy, but this percentage decreases year by year.⁴⁸

In a follow-up of cholelithiasis patients with mild or nonspecific symptoms ($n = 153$), acute gallstone complication was observed in 15% ($n = 23$) and acute cholecystitis was seen in 12% ($n = 18$) (level 4).⁴⁹ According to another report, on the follow-up of the patients with asymptomatic cholelithiasis ($n = 600$), 16% (96) of them presented with some symptoms (average period of observation until the manifestation of symptom, 29.8 months) during the follow-up period, while 3.8% (23 patients) presented with acute cholecystitis. The rate of change from asymptomatic to symptomatic cholelithiasis is highest during the first 3 years after diagnosis (15%–26%), but then declines (level 4). However, there is a report suggesting that there is no difference in the incidence of common symptoms such as heartburn and upper abdominal pain, in cholelithiasis patients between those patients with asymptomatic cholelithiasis and controls without gallstones (level 2b).⁵⁰

AIDS as a risk factor. Enlarged liver and/or abnormal liver functions are observed in two-thirds of AIDS patients, some of whom have biliary tract disease. Biliary disease may occur by two mechanisms in AIDS patients: via AIDS cholangiopathy (which is more fre-

quent) and via acute acalculous cholecystitis; AIDS patients with sclerosing cholangitis are also seen.

AIDS cholangiopathy is often observed in middle-aged male patients who have had AIDS for more than 1 year (average disease period, 15 ± 2.2 months; average age, 37 years [range, 21 to 59 years]). Ninety percent of the patients complain of upper abdominal pain and have enlarged intra- and extrahepatic bile ducts on abdominal ultrasonography. Abnormal findings on abdominal ultrasonography and computed tomography are seen in 81% and 78% of patients, respectively. Biochemical tests show a marked increase in the level of alkaline phosphatase (level 4).⁵¹

Acalculous cholecystitis in AIDS patients is characterized by: (1) younger age than in non-AIDS patients, (2) problems with oral ingestion (3), right upper abdominal pain, (4) a marked increase in alkaline phosphatase and a mild increase in serum bilirubin level, and (5) association with cytomegalovirus and cryptosporidium infections (level 4).⁵¹ According to a review of abdominal surgery for AIDS patients, acute cholecystitis is the most frequent reason for performing open surgery in AIDS patients.⁵²

Drugs as etiologic agents. According to the review by Michielsen et al.,⁵³ regarding the association between drugs and acute cholecystitis, 90%–95% of acute cholecystitis cases are caused by cholelithiasis, and drugs promoting the formation of stones are indirectly associated with a risk of acute cholecystitis (level 4). The etiological mechanism of drug-associated gallbladder diseases, as discussed in the review,⁵³ is shown in Table 7.

Table 6. Natural history of asymptomatic, mildly symptomatic, and symptomatic cholelithiasis patients

Author	Characteristic	No. of cases	Average follow-up period (years)	No. of acute cholecystitis cases (%)	Only those with remarkable jaundice (%)		Gallbladder cancer	
					Cholangitis	Cholecystitis	Cholangitis	Cholecystitis
Comfort et al.	Asymptomatic	112	15	0	0	0	0	0
Lund	Asymptomatic	95	13	?	?	1 (?)	0	0
Gracie et al.	Asymptomatic	123	11	2	0	0	1	0
McSherry et al.	Asymptomatic	135	5	3	0	0	0	0
Friedman et al.	Asymptomatic	123	7	4	2	2	0	0
Thistle et al.	Asymptomatic	305	2	≥3	0	0	0	0
Wenckert et al.	+ Symptomatic							
	Mildly symptomatic	781	11	81 (10.4)	<59 ^a	0	<59 ^a	3
Ralston et al.	Mildly symptomatic	116	22	?	?	?	?	2
Friedman et al.	Mildly symptomatic	344	9	20 (5.8)	10	1	3	2
Newman et al.	Symptomatic	332	10	38 (11.4)	?	?	1	2
McSherry et al.	Symptomatic	556	7	47 (8.5)	19	0	0	1

Review by Friedman⁴⁸

^aIn this report, 59 cases were diagnosed as jaundice and/or acute pancreatitis, based on serum bilirubin and amylase values

Table 7. Etiological mechanisms of gallbladder diseases

Etiological mechanism	Drug/Treatment
Direct chemical toxicity	Hepatic artery infusion
Promotion of stone formation by bile	
Inhibition of ACAT activity	Progesterone, fibrate
Increased hepatic lipoprotein receptors	Estrogen
Induction of acute cholecystitis in patients with cholelithiasis	Thiazides (unconfirmed)
Promotion of calcium salt precipitation in bile	Ceftriaxone octreotide
Altered mobility of the gallbladder	Narcoid Anticholinergic drugs
Promotion of hemolysis	Dapsone
Immunological mechanism	Antimicrobial drugs (erythromycin, ampicillin) Immunotherapy

Review by Michielsen et al.⁵³

It is reported that women taking oral contraceptives have a higher risk of having gallbladder disease, but there also is a report which denies the association between the disease and these drugs (level 2a).⁵⁴ Among various drugs used for the treatment of hyperlipidemia, only fibrate is shown to be associated with gallstone diseases (level 2b).⁵⁵ One report suggests that thiazides induce acute cholecystitis (level 3b),⁵⁶ and another report denies this association (level 3b).⁵⁷ The administration of a large dose of ceftriaxone, a third-generation cephalosporin antimicrobial, in infants, precipitates calcium salt in bile and forms a sludge in 25%–45% of them, but these effects disappear when the medication is discontinued (level 4).⁵³ It is reported that the long-term administration of octreotide causes cholestasis, and that administration for a year causes cholelithiasis in 50% of patients (level 4).⁵³ Hepatic artery infusion will cause chemical cholecystitis (level 4).⁵³ Erythromycin and ampicillin are reported to be a cause of hypersensitive cholecystitis (level 4).⁵³ According to a meta-analysis of the risk of disease induced by hormone replacement therapy, the relative risks (RRs) of cholecystitis were 1.8 (95% confidence interval [CI], 1.6–2.0) and 2.5 (95% CI, 2.0–2.9) at less than 5 years of treatment and at 5 and more years, respectively (level 1a).⁵⁸

Ascaris as an etiologic factor. The complications of ascariasis include hepatic, biliary, and pancreatic diseases. Complications in the biliary tract include: (1) cholelithiasis with the ascarid as a nidus for stone formation, (2) acalculous cholecystitis (3), acute cholangitis (4), acute pancreatitis, and (5) hepatic abscess.⁵⁹ Biliary tract disease is caused by the obstruction of the hepatic and biliary tracts by the entry of ascarids from the duodenum through the papilla. Ascarids entering the biliary tract usually return to the duodenum in a week, but if

they stay over 10 days there, they will die and form a nidus for stone formation.

Ascarid-associated biliary diseases occur more frequently in women (male/female ratio, 1:3) and less frequently in infants. The risk of biliary complications is higher in pregnant than in non-pregnant women (level 4).⁵⁹ In epidemic regions such as China and Southeast Asia, ascariasis is a frequent cause of cholelithiasis.⁵⁹

Role of pregnancy. The risk of cholelithiasis in women begins to increase when adolescence begins and it declines when the menopause begins. It is also said that the use of oral contraceptives is correlated with a risk of gallbladder disease. It is considered, therefore, that levels of estrogen and progesterone are involved in the formation of gallstones.⁶⁰ Cholecystitis is the second most common cause of acute abdomen, following appendicitis, in pregnant women, and occurs in one of 1600 to 10000 pregnant women (level 4).⁶⁰ Cholelithiasis is the most frequent cause of cholecystitis in pregnancy and accounts for 90% or more of all causes of cholecystitis (level 4).⁶⁰ Routine ultrasonography found cholelithiasis in 3.5% of pregnant women (level 4),⁶⁰ but it is unknown whether pregnancy increases the risk of cholecystitis. The frequency of cholecystectomy in pregnant women is lower than that in non-pregnant women. This is not because of the lower incidence of cholecystectomy in pregnant women, but because physicians tend to refrain from performing any operation during pregnancy. Though there are few reports of patients undergoing cholecystectomy during pregnancy, there is no evidence that laparoscopic surgery increases the maternal or fetal risks (level 2c).⁶¹

Acute cholecystitis and four (or five) “Fs”. It has been said that the patients with cholelithiasis have factors such as “4F” and “5F” (fair, fat, female, fertile, and

forty). Common to all individuals with these “4/5Fs” are high levels of estrogen and progesterone.

According to the Framingham Study, which examined the risk factors for cholelithiasis in a 10-year follow-up study of 30- to 59-year-old subjects, the risk of cholelithiasis within 10 years was highest among the 55- to 62-year-old age group, and most of the patients were diagnosed with cholelithiasis in their fifties and sixties. Although the incidence of cholelithiasis in female patients of all age groups is more than double that of male patients, the difference between the incidence in men and women tends to shrink with increasing age (level 1b).⁶²

Cholelithiasis is one of the main diseases associated with obesity. The Framingham study also confirms that cholelithiasis patients tend to be more obese than non-cholelithiasis patients (level 2a).⁶² However, there is a report that this tendency is much more prominent in female than in male patients.⁶³ Not only obesity but also dieting is associated with the risk of cholelithiasis. Drastic dieting increases the risk of cholelithiasis in obese people (level 2b).^{64–67} The incidences of both cholelithiasis and cholecystitis in obese people (age, 37–60 years; women with a body mass index [BMI] of 34 or higher and men with a BMI of 38 or more) are significantly higher than those in non-obese people (cholelithiasis, 5.8% vs 1.5%; Odds ratio [OR], 4.9; women 6.4% vs 2.6%; OR, 4.7; cholecystitis, 0.8% vs 3.4%; OR, 5.2; women 4.0% vs 11.2%; OR, 3.4) (level 2b).⁶⁸

The Framingham Study indicates that the number of pregnancies in those patients who had cholelithiasis at entry into a cohort or those in whom the symptoms of cholelithiasis appeared within 10 years, was significantly higher than the number of pregnancies in subjects not fulfilling these criteria (level 2b).⁶²

Though the association of “4F” and “5F” with cholelithiasis has been relatively closely examined, no study has examined the association of factors other than obesity and age with the risk of onset of acute cholecystitis.

Pathophysiology

In the majority of patients, gallstones are the cause of acute cholecystitis. The process is one of physical obstruction of the gallbladder by a gallstone, at the neck or in the cystic duct. This obstruction results in increased pressure in the gallbladder. There are two factors which determine the progression to acute cholecystitis — the degree of obstruction and the duration of the obstruction. If the obstruction is partial and of short duration the patient experiences biliary colic. If the obstruction is complete and of long duration the patient develops acute cholecystitis. If the patient does not receive early treatment, the disease becomes more serious and complications occur.

Pathological classification

Edematous cholecystitis: first stage (2–4 days). The gallbladder has interstitial fluid with dilated capillaries and lymphatics. The gallbladder wall is edematous. The gallbladder tissue is intact histologically, with edema in the subserosal layer.

Necrotizing cholecystitis: second stage (3–5 days). The gallbladder has edematous changes with areas of hemorrhage and necrosis. When the gallbladder wall is subjected to elevated internal pressure, the blood flow is obstructed, with histological evidence of vascular thrombosis and occlusion. There are areas of scattered necrosis, but it is superficial and does not involve the full thickness of the gallbladder wall.

Suppurative cholecystitis: third stage (7–10 days). The gallbladder wall has white blood cells present, with areas of necrosis and suppuration. In this stage, the active repair process of inflammation is evident. The enlarged gallbladder begins to contract and the wall is thickened due to fibrous proliferation. Intrawall abscesses are present and involve the entire thickness of the wall. Pericholecystic abscesses are present.

Chronic cholecystitis. Chronic cholecystitis occurs after the repeated occurrence of mild attacks of cholecystitis, and is characterized by mucosal atrophy and fibrosis of the gallbladder wall. It can also be caused by chronic irritation by large gallstones and may often induce acute cholecystitis.

Specific forms of acute cholecystitis. There are four specific forms of acute cholecystitis: (1) acalculous cholecystitis, which is acute cholecystitis without cholelithiasis; (2) xanthogranulomatous cholecystitis, which is characterized by the xanthogranulomatous thickening of the gallbladder wall and elevated intra-gallbladder pressure due to stones, with rupture of the the Rokitansky-Achoff sinuses. This rupture causes leakage and bile entry into the gallbladder wall. The bile is ingested by histocytes, forming granulomas consisting of foamy histocytes. Patients usually have symptoms of acute cholecystitis in the initial stage. (3) emphysematous cholecystitis, in which air appears in the gallbladder wall due to infection with gas-forming anaerobes, including *Clostridium perfringens*. This form is likely to progress to sepsis and gangrenous cholecystitis; it is often seen in diabetic patients. (4) Torsion of the gallbladder.⁶⁹ Torsion of the gallbladder is known to occur by inherent, acquired, and other physical causes. An inherent factor is a floating gallbladder, which is very mobile because the gallbladder and cystic ducts are connected with the liver by a fused ligament. Acquired factors in-

clude splanchnoptosis, senile humpback, scoliosis, and weight loss. Physical factors causing torsion of the gallbladder include sudden changes of intraperitoneal pressure, sudden changes of body position, a pendulum-like movement in the anteflexion position, hyperperistalsis of organs near the gallbladder, defecation, and trauma to the abdomen.

Incidence of complications with advanced forms of acute cholecystitis

The incidence of complications with advanced forms of acute cholecystitis ranges widely, from 7.2% to 26%, in reports published since 1990.^{70–74} In patients with acute cholecystitis ($n = 368$), the incidence of morbidity was 17%, with the incidences of gangrenous, suppurative, perforating, and emphysematous cholecystitis being 7.1%, 6.3%, 3.3%, and 0.5%, respectively.⁷⁴

Types of complications. There are four types of complications. (1) Perforation of the gallbladder, which is caused by acute cholecystitis, injury, or tumors, and occurs most often as a result of ischemia and necrosis of the gallbladder wall. (2) Biliary peritonitis, which occurs with the entry into the peritoneal cavity of bile leaked due to various causes, including cholecystitis-induced gallbladder perforation, trauma, a catheter detached during biliary drainage, and incomplete suture after biliary operation. (3) Pericholecystic abscess, a morbid condition in which a perforation of the gallbladder wall is covered by the surrounding tissue, with the formation of an abscess around the gallbladder. (4) Biliary fistula, which can occur between the gallbladder and the duodenum following an episode of acute cholecystitis. The fistula is usually caused by a large gallbladder stone eroding through the wall of the gallbladder into the duodenum. If the stone is large, the patient can develop gallstone ileus, with the stone causing mechanical small-bowel obstruction at the ileocecal valve.

Prognosis

The mortality in patients with acute cholecystitis is 0–10%^{75–81} (Table 8), whereas the mortality in patients with postoperative cholecystitis and acalculous cholecystitis is as high as 23%–40%.^{82–84} The mortality of elderly patients (75 years and older) tends to be higher than that of younger patients,^{85,86} and a comorbidity such as diabetes may increase the risk of death.⁷⁵ Many reports of the mortality and morbidity of acute cholecystitis are difficult to compare, because there are significant variations in the diagnostic criteria, timing and type of operation, presence of comorbidities, and hospital support systems for critically ill patients, as well as variations in available surgical expertise.

According to reports published in 1980 and before, most of the causes of death after cholecystectomy were related to postoperative infections, such as ascending cholangitis, hepatic abscess, and sepsis.^{76,77} Since 1980, postoperative mortality from infection has decreased and the major causes of death include myocardial infarction, cardiac failure, and pulmonary infarction.^{78,79} Cholecystostomy was a common form of treatment in 1970 and before, and the most common cause of death during that period was pneumonia and sepsis.⁸⁷ Currently, the major causes of death following cholecystostomy include malignant tumor, respiratory failure, and cardiac failure.^{88,89}

Recurrence rate of acute cholecystitis after conservative treatment

Most patients with acute cholecystitis are treated with a cholecystectomy, and it is difficult to anticipate whether the outcome will show recurrence. Recurrences of clinical concern include the recurrence of (1) acute cholecystitis after spontaneous recovery without the undergoing of any treatment; (2) acute cholecystitis while waiting for cholecystectomy after conservative treatment with diet modification and antibiotics; (3) acute

Table 8. Mortality of acute cholecystitis

Author	Period	Country	Subjects	No. of cases	Mortality (%)
Meyer ⁷⁶	1958–1964	USA		245	4.49
Ranasohoff ⁷⁵	1960–1981	USA		298	3.36
Gagic ⁷⁷	1966–1971	USA		93	9.68
Girard and Moria ⁷⁸	1970–1986	Canada		1691	0.65
Addison and Finan ⁷⁹	1971–1990	UK		236	4.66
Bedirli ⁸⁰	1991–1994	Turkey		368	2.72
Gharaibeh ⁸¹	1993–1900	Jordan		204	0
Hafif ⁸⁵	1952–1967	Israel	Age, 70 years and older	131	3.82
Gingrich ⁸⁷	1976–1985	USA	Only external biliary drainage	114	32
Glenn ⁸⁶	1977–1987	USA	Age, 65 years old and older	655	9.92
Kalliafas ⁸²	1981–1987	USA	Acalculous cases only	27	40.74
Inoue and Mishima ⁸³	1989–1993	Japan	Postoperative cases only	494	23.08
Savoca ⁸⁴	1994–1999	USA	Acalculous cases only	47	6.38

cholecystitis when cholecystectomy is not performed for some reason, such as surgical risk or the patient's decision (with or without biliary drainage); and (4) cholangitis after cholecystectomy.

There are no data on the recurrence of acute cholecystitis after resolution of the initial symptoms. The recurrence of acute cholecystitis while patients are waiting for cholecystectomy following conservative treatment ranges from 2.5% to 22%.^{75,90} In 311 patients with acute calculous cholecystitis, 25 of 39 patients who did not have a cholecystectomy during the acute stage were scheduled to undergo delayed operation after being discharged from hospital. Only 1 of the 25 patients (2.5%) developed recurrent acute cholecystitis while waiting for an operation.⁷⁵ In non-severe cases, acute cholecystitis recurred in 2% of patients within an 8- to 10-week waiting period, 6% of whom showed gallbladder perforation.⁹⁰

Long-term recurrence is reported to be 10%–50% in 6 months to several years of observation, though there are few reports. According to a randomized controlled trial comparing non-operative treatment and cholecystectomy for patients with acute cholecystitis, excluding those with severe cases ($n = 56$), 11% had a history of acute cholecystitis, and 8 (24%) of 33 patients assigned to non-operative treatment underwent cholecystectomy during an observation period of 1.5–4 years.⁹¹ In patients with acute cholecystitis who were observed after treatment with percutaneous drainage, acute cholecystitis recurred once or more in 28 of 60 patients (47%) during an average observation period of 18 months,⁸⁸ and it recurred once or more in 11 of 36 (31%) patients who were observed for 37 months on average.⁸⁹ In a report of 114 patients who underwent only cholecystoscopy, among 585 patients who were hospitalized because of acute cholecystitis, acute cholecystitis recurred in 5 of 23 patients observed for 6 months to 14 years and 14 of the 23 patients remained asymptomatic.⁹²

Acknowledgments. We would like to express our deep gratitude to the Japanese Society for Abdominal Emergency Medicine, the Japan Biliary Association, and the Japanese Society of Hepato-Biliary-Pancreatic Surgery, who provided us with great support and guidance in the preparation of the Guidelines. This process was conducted as part of the project for the Preparation and Diffusion of Guidelines for the Management of Acute Cholangitis (H-15-Medicine-30), with a research subsidy for fiscal 2003 and 2004 (Integrated Research Project for Assessing Medical Technology) sponsored by the Japanese Ministry of Health, Labour, and Welfare.

We also truly appreciate the panelists who cooperated with and contributed significantly to the International Consensus Meeting, held on April 1 and 2, 2006.

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