TG13 current terminology, etiology, and epidemiology of acute cholangitis and cholecystitis

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Abstract While referring to the evidence adopted in the Tokyo Guidelines 2007 (TG07) as well as subsequently obtained evidence, further discussion took place on terminology, etiology, and epidemiological data. In particular, new findings have accumulated on the occurrence of symptoms in patients with gallstones, frequency of severe cholecystitis and cholangitis, onset of cholecystitis and cholangitis after endoscopic retrograde cholangiopancreatography and medications, mortality rate, and recurrence rate. The primary etiology of acute cholangitis/

cholecystitis is the presence of stones. Next to stones, the most significant etiology of acute cholangitis is benign/malignant stenosis of the biliary tract. On the other hand, there is another type of acute cholecystitis, acute acalculous cholecystitis, in which stones are not involved as causative factors. Risk factors for acute acalculous cholecystitis include surgery, trauma, burn, and parenteral nutrition. After 2000, the mortality rate of acute cholangitis has been about 10 %, while that of acute cholecystitis has generally been less than 1 %. After the publication of TG07, diagnostic criteria and severity assessment criteria were standardized, and the distribution of cases according to severity and comparison of clinical data among target populations have become more subjective. The concept of

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healthcare-associated infections is important in the current treatment of infection. The treatment of acute cholangitis and cholecystitis substantially differs from that of community-acquired infections. Cholangitis and cholecystitis as healthcare-associated infections are clearly described in the updated Tokyo Guidelines (TG13).

Free full-text articles and a mobile application of TG13 are available via http://www.jshbps.jp/en/guideline/tg13.html.

Introduction

Acute biliary infection comprises manifold disease concepts and is mostly separated into [1] acute cholangitis, a systemic infectious disease that is occasionally life-threatening and requires immediate treatment, and [2] acute cholecystitis, frequently presenting a mild clinical course.

The definition, pathophysiology, and epidemiology of acute cholangitis are presented in the Tokyo Guidelines for the management of acute cholangitis and chlecystitis 2007 (TG07) [1], while the updated Tokyo Guidelines (TG13) present more subjective data acquired throughout the revision of TG07. As for the data of current clinical trials in particular, the data concerning frequency of severe cases,

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mortality rate, and recurrence rate are introduced along with epidemiological data.

Terminology

Acute cholangitis

Definition

Acute cholangitis is a morbid condition with acute inflammation and infection in the bile duct [1, 2].

Pathophysiology

The onset of acute cholangitis involves two factors: (1) increased bacteria in the bile duct, and (2) elevated intraductal pressure in the bile duct allowing translocation of bacteria or endotoxin into the vascular and lymphatic system (cholangio-venous/lymphatic reflux). Because of its anatomical characteristics, the biliary system is likely to be affected by the elevated intraductal pressure. In acute cholangitis, bile ductules tend to become more permeable to the translocation of bacteria and toxins with the elevated intraductal biliary pressure. This process results in serious and fatal infections such as hepatic abscess and sepsis [1].

Historical aspect of terminology

Signs of hepatic fever Hepatic fever was a term used for the first time by Charcot in his report published in 1887 [3]. Intermittent fever accompanied by chills, right upper quadrant abdominal pain, and jaundice have been established as Charcot's triad.

Acute obstructive cholangitis Acute obstructive cholangitis was defined by Reynolds and Dargan [4] 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 emergency surgical biliary decompression was the only effective procedure for treating the disease. These five symptoms were thus called Reynold's pentad.

Longmire's classification Longmire classified patients with three characteristics of intermittent fever accompanied by chills and shivering, right upper quadrant abdominal pain, and jaundice as acute suppurative cholangitis, and those with lethargy or mental confusion and shock along with the triad as acute obstructive suppurative cholangitis (AOSC). He also reported that the latter corresponded to the morbidity of acute obstructive cholangitis as defined by Reynolds [5].

However, terms such as acute obstructive cholangitis and acute obstructive suppurative cholangitis (AOSC) are not appropriate as current clinical terminology because their definition is conceptual and ambiguous.

Acute cholangitis/cholecystitis as healthcare-associated infections

In the US IDSA/SIS guidelines on abdominal infection, acute cholangitis/cholecystitis refers to biliary tract infection that has developed in any of the following patients: patients with a history of less than 12 months hospital stay, patients undergoing dialysis, patients staying at nursing home/rehabilitation facility, and patients in an immune-compromised state [6].

That concept has been extrapolated, and acute cholangitis/cholecystitis as a healthcare-associated infection in Japan refers to infection that has developed in patients (long-term recumbency, admission to nursing home, gastrostomy, tracheostomy, repeated aspiration pneumonia, bed sore, urethral catheter placement, history of recent postoperative infection, or undergoing antimicrobial therapy due to other diseases) at risk of having resistant bacteria (bacteria with a high minimum inhibitory concentration, MIC). Those infections should be treated independently from community-required infections.
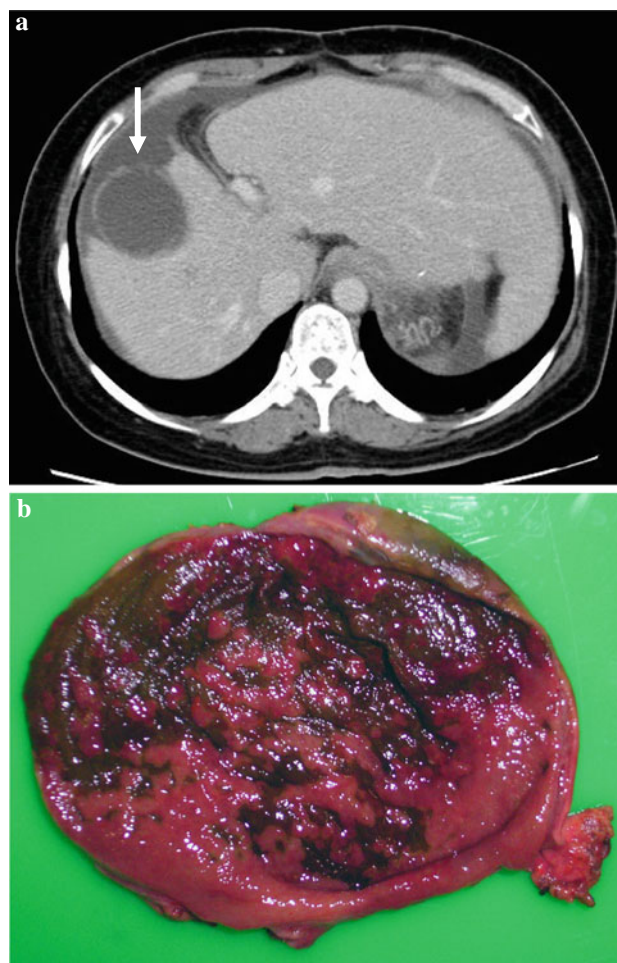
Acute cholecystitis

Definition

Acute inflammatory disease of the gallbladder, often attributable to gallstones, but many factors, such as ischemia, motility disorders, direct chemical injury, infections by microorganism, protozoon and parasites, collagen disease, and allergic reaction are also involved [1].

Pathophysiology

In the majority of patients, gallstones are the cause of acute cholecystitis. The process is one of physical obstruction of the gallbladder at the neck or in the cystic duct by a gallstone. 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 can occur [1].

Pathological classification

(1) *Edematous cholecystitis: 1st stage (2–4 days)* The gallbladder has interstitial fluid with dilated capillaries and lymphatics. The gallbladder wall is edematous. Gallbladder tissue is intact histologically with edema in the subserosal layer [1].

(2) *Necrotizing cholecystitis: 2nd stage (3–5 days)* The gallbladder has edematous changes with areas of hemorrhage and necrosis. When the gallbladder wall is subject to elevated internal pressure, the blood flow is obstructed with histological evidence of vascular thrombosis and occlusion. There are areas of scattered necrosis but they are superficial and do not involve the full thickness of the gallbladder wall [1] (Fig. 1).

Fig. 1 Necrotizing cholecystitis. **a** Contrast-enhanced CT images show discontinuity of the gallbladder wall, suggesting possible presence of necrosis in a portion of the wall. **b** Resected specimen showing extensive falling-off of the gallbladder membrane, erosion, ulcer, and exposed fascia. Histologically, necrosis of the gallbladder wall and suppurative inflammation accompanying abscess (data not shown) were observed with fibrillation and regenerating hyperplastic epithelium as background

(3) *Suppurative cholecystitis: 3rd stage (7–10 days)* The gallbladder wall has white blood cells that present areas of necrosis and suppuration. In this stage, the active repairing process of inflammation is evident. The enlarged gallbladder begins to contract and the wall is thickened due to fibrous proliferation. Intramural abscesses are observed and do not involve the entire thickness of the wall. Pericholecystic abscesses are also present [1] (Fig. 2).

(4) *Chronic cholecystitis:* Chronic cholecystitis occurs after the repeated occurrence of mild cholecystitis attacks, and is characterized by mucosal atrophy and fibrosis of the gallbladder wall. It can also be caused by the chronic irritation of large gallstones and may often induce acute cholecystitis [1]. Acute on chronic cholecystitis refers to acute infection that has occurred in chronic cholecystitis [7, 8] (Fig. 3). Histologically, neutrophil invasion is observed in the gallbladder wall with chronic cholecystitis accompanying lymphocyte/plasma cell infiltration and fibrosis.

Special forms of acute cholecystitis

(1) *Acalculous cholecystitis:* Acute cholecystitis without cholecystolithiasis

(2) *Xanthogranulomatous cholecystitis:* Cholecystitis characterized by xanthogranulomatous thickening of the gallbladder wall [9] and elevated intra-gallbladder pressure due to stones with a rupture of the Rokitansky–Achoff sinuses. This causes leakage and entry of bile into the gallbladder wall. It is ingested by histocytes to form granulomas consisting of foamy histocytes. Patients usually have symptoms of acute cholecystitis in the initial stage.

(3) *Emphysematous cholecystitis:* In emphysematous cholecystitis, air appears in the gallbladder wall due to infection by gas-forming anerobes including *Clostridium perfringens*. It is often seen in diabetic patients, and is likely to progress to sepsis and gangrenous cholecystitis [1].

(4) *Torsion of the gallbladder:* Cause of acute cholecystitis [10]. Torsion of the gallbladder is known to occur by inherited, acquired, and other physical causes. The inherited factor is the floating gallbladder, which is very mobile because the gallbladder and cystic ducts are connected with the liver by a fused ligament. The acquired factors include splanchnoptosis, senile humpback, scoliosis, and weight loss. Physical factors causing torsion of the gallbladder include sudden change of intraperitoneal pressure, sudden change of body position, pendulum-like movement in the anteflexion position, hyperperistalsis of the organs near the gallbladder, defecation, and blow to the abdomen.

Advanced forms of and the type of complications of acute cholecystitis [1]

(1) *Perforation of gallbladder:* Perforation of the gallbladder is caused by acute cholecystitis, injury, or tumors, and occurs most frequently as a result of ischemia and necrosis of the gallbladder wall.

(2) *Biliary peritonitis:* Biliary peritonitis occurs with the entry into the peritoneal cavity of bile leakage due to various causes including cholecystitis-induced gallbladder perforation, trauma, and a detached catheter during biliary drainage and incomplete suture after biliary operation.

(3) *Pericholecystic abscess:* A morbid condition in which perforation of the gallbladder wall is covered by the surrounding tissues along with the formation of abscesses around the gallbladder

(4) *Biliary fistula:* A biliary fistula can occur between the gallbladder and the duodenum following an episode of acute cholecystitis. This is usually caused by a large gallbladder stone eroding through the wall of the gallbladder into the duodenum. If the stone is large in size, the patient can develop gallstone ileus with the stone causing mechanical small bowel obstruction at the ileocecal valve.

Frequency of symptom appearance

Incidence

Q1. What is the incidence proportion of the appearance of symptoms in patients with asymptomatic gallstones or those with mild gallstones?

| Asymptomatic, mild symptom- patients ;	~40 %/5-10years
Acute cholangitis ;	0.3 ~ 1.6 %
Acute cholecystitis ;	3.8 ~ 12%
Annual proportion;	1~3%/year

Incidence in patients with gallstones

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 Ministry of Health and Welfare), the number of cases with acute cholecystitis has increased from 3.9
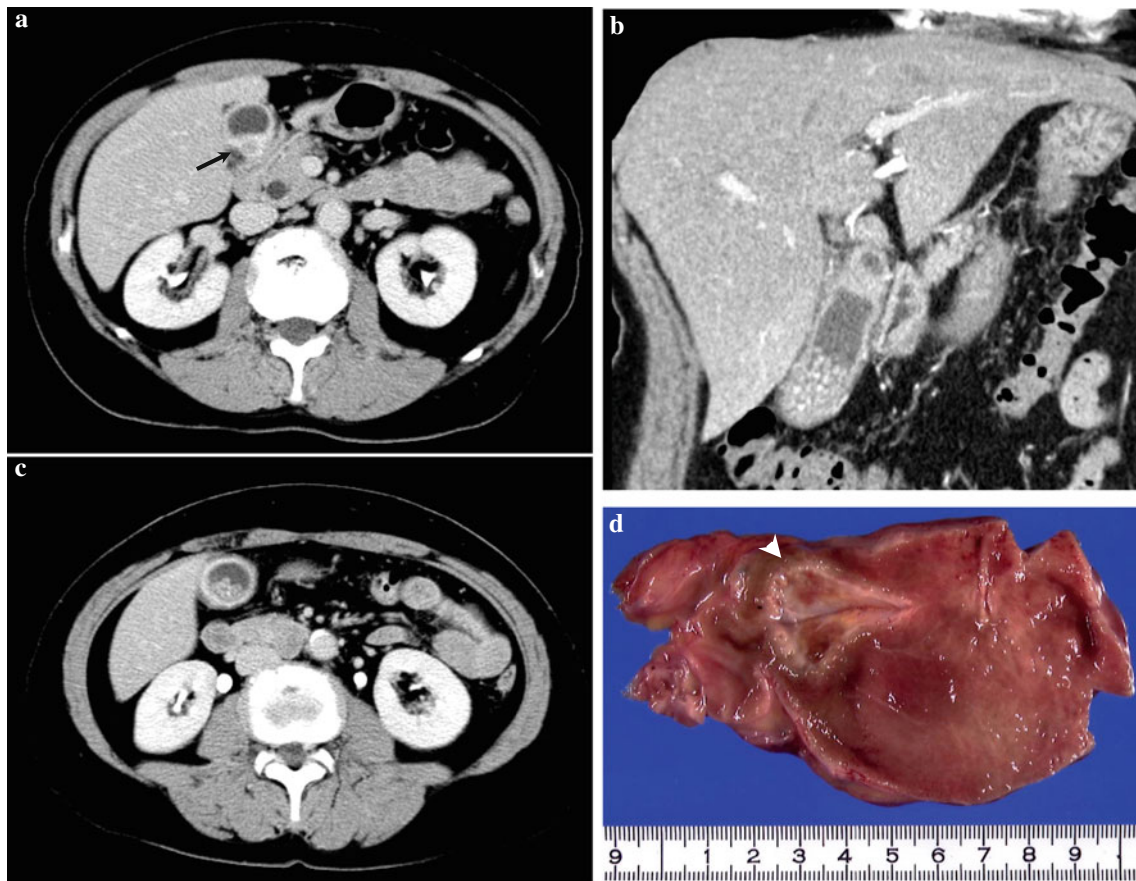
Fig. 2 Suppurative cholecystitis. **a** Contrast-enhanced CT visualizing the gallbladder wall under extrinsic compression (*up arrow*) suggests possible presence of abscess in a portion of the gallbladder wall. **b–c** Many minute stones were observed within the gallbladder. **d** The resected specimen shows the gallbladder membrane accompanying extensive abscess formation within the wall (*arrowhead*)
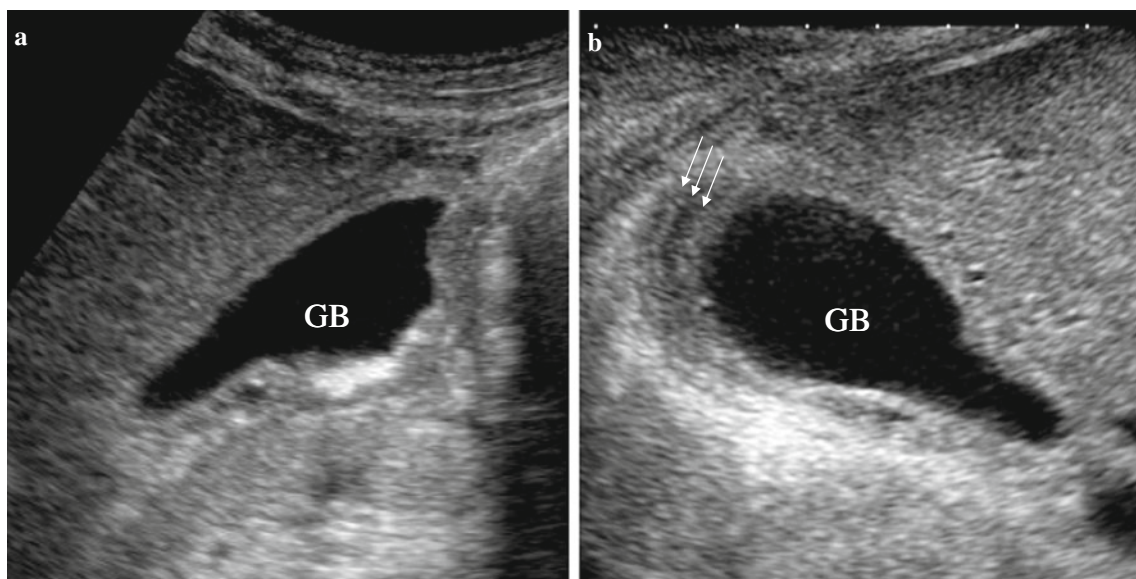
Fig. 3 US images of acute-on-chronic cholecystitis patients. **a** The gallbladder wall is shown to have thickened prior to the onset of acute inflammation. **b** The gallbladder itself continued to swell after the onset of acute inflammation and the wall has further thickened along with striated intraluminal lucency (*up arrow*). Only by comparing the images before (**a**) and after (**b**) the onset of acute inflammation can a decision of the wall thickening and the swelling of gallbladder be correctly made

Table 1 Natural history of asymptomatic, mildly symptomatic, and symptomatic cholelithiasis patients

References	Characteristic	No. of cases	Average follow-up period (years)	No. of acute cholecystitis cases (%)	Only those with remarkable jaundice cases (%)	Cholangitis	Cholecystitis	Gallbladder cancer
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 + symptomatic	305	2	≥3	0	0	0	0
Wenckert et al.	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 Friedman [12]

[a] In this report, 59 cases were diagnosed as jaundice and/or acute pancreatitis based on the serum bilirubin and amylase values

million in 1979 to over 10 million in 1993 (Public Welfare Index in Japan, 1993). No large epidemiological study has been conducted to date, but it can be estimated that approximately 10 % of the general population have gallstones [11].

Natural history of patients with asymptomatic gallstones

According to a review by Friedman, 1–2 % of patients with asymptomatic gallstones and 1–3 % of patients with mild symptoms annually presented severe symptoms or complications (acute cholecystitis, acute cholangitis, severe jaundice, or pancreatitis (Table 1)). The risk of such complications was high during the first few years after gallstones had been detected and it decreased subsequently. The probability of undergoing operation due to subsequent severe symptoms was 6–8 %/year in patients initially presenting moderate symptoms and the symptoms decreased year by year [12]. Observational studies involving patients with mild cholecystolithiasis have found that, during 5–7 years' observation, 15 % of the subjects presenting mild or nonspecific symptoms developed complications associated with gallstones, 12 % developed acute cholecystitis (n = 153), 21.9 % of the subjects were without symptoms during 8.7 years'

observation (median), and 42 % of those with mild symptoms developed abdominal pain of higher than mild severity (n = 856), respectively. The above data show that 20–40 % of patients with asymptomatic cholelithiasis have a risk for developing some type of symptoms/signs (1–3 % annually) [12–18].

Incidence of severe cases of acute cholecystitis and cholangitis

Q2. What is the incidence proportion of severe cases of acute cholangitis?

> **The proportion of severe cases is 12.3 % based on the severity assessment criteria of TG07**

Severe cases (grade III) in TG07 refer to those having poor prognostic factors including shock, consciousness disturbance, organ failure, and disseminated intravascular coagulation. The definition was ambiguous before the publication of TG07, which, after review of the frequency

of acute cholangitis, reported that the incidence of severe cases was 7–25.5 % for shock, 7–22.2 % for consciousness disturbance, and 3.5–7.7 % for Reynold's pentad [19].

The proportion of cases diagnosed as severe (grade III) according to the TG07 severity assessment criteria was 12.3 % or 23 of the 187 cases of acute cholangitis due to bile duct stones [20].

Q3. What is the proportion of severe cases of acute cholecystitis?

> The proportion of severe cases (accompanying organ dysfunction) is 6.0% according to TG07 severity assessment criteria.

"Severe" in TG07 refers to acute cholecystitis accompanying organ dysfunction (grade III), and the proportion of the above cases was 6.0 % (14 of 235 cases) [21].

Acute cholangitis and cholecystitis as complications following ERCP

Q4. What is the proportion of acute cholangitis and cholecystitis following ERCP?

> Acute cholangitis; 0.5~2.4 %
> Acute cholecystitis; 0.2~1.0 %

The incidence of complications following endoscopic retrograde cholangiopancreatography (ERCP) is 0.8–12.1 % and the mortality rate is 0.0023–1.5 % [22–37]. The most frequently encountered complication is acute pancreatitis, although mild to moderate cases account for the greater part (Supplementary Table 1).

The proportion of acute cholangitis and cholecystitis after ERCP is 0.5–2.4 % for cholangitis and 0.2–1.0 % for cholecystitis [22–26, 29–33].

There are differences in the proportion of complications between diagnostic ERCP and therapeutic ERCP, and those of cholangitis and overall complications associated with therapeutic ERCP are more likely to become elevated [31, 33, 42].

Due to the diffusion of procedures and improved techniques of operators, complications following ERCP have increased in recent years, although no change has been observed in the frequency of the occurrence of acute cholecystitis, so its occurrence is unpredictable [31].

Etiology

Acute cholangitis

Q5. What are the etiology and mechanism of acute cholangitis?

> Acute cholangitis occurs as results of a biliary tract obstruction (cholestasis) and bacterial growth in bile (bile infection).

The onset of acute cholangitis requires two factors, [1] biliary obstruction and [2] bacterial growth in bile (bile infection). Causes of frequent biliary obstruction are choledocholithiasis, benign biliary stenosis, stricture of the biliary anastomosis, and stenosis by malignant diseases [38, 39]. Choledocholithiasis used to be the most frequent cause, 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 with acute cholangitis [38, 39]. Tables 2 and 3 show the results of studies on the causes of acute cholangitis.

Table 2 Etiology of acute cholangitis

Cholelithiasis
Benign biliarystricture
Congenital factors
Post-operative 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

Reviewed by Kimura et al. [1]

Acute cholecystitis

Q6. What are the etiology and mechanism of acute cholecystitis?

> Etiology ; Cystic duct obstruction (Galltones are involved in 90〜95 % of the causes.)
> Mechanism ; Bile stasis, activation of inflammatory mediators and mucosal injuries

Gallstones account for 90–95 % of the causes of acute cholecystitis [46–49]. Following cystic duct obstruction and cholestasis within the gallbladder due to the torsion of stones, gallbladder mucosa disorder occurs, thereby inducing the activation of infectious mediator [50]. On the other hand, acute acalculous cholecystitis accounts for 3.7–14 % of acute cholecystitis [51–55]. Risk factors include surgery, trauma, long-term intensive care unit stay, infection, thermal burn, and parenteral nutrition [56, 57].

Risk factors

Q7. What are the factors for which association with the development of acute cholangitis/cholecystitis is suggested?

> Obesity; Acute cholecystitis
> Medication;
>   Hormone replacement therapy: Increased risk for the development of cholecystitis or cholecystectomy
>   Statin: Decreased risk for carrying out cholecystectomy

"4Fs" and "5Fs"

Acute cholecystitis and four (or five) "Fs"

The "4Fs" (forties, female, fat, fair) and "5Fs" (4Fs plus fecund or fertile) have been shown to be associated with lithogenesis in the gallbladder [50]. However, it has not been established whether or not all these factors are associated with the development of acute cholangitis/cholecystitis.

Age and female gender

There is no evidence to suggest the association of age/sex with the onset of acute cholangitis/cholecystitis.

According to the Framingham study which examined risk factors of cholelithiasis in subjects 30–59 years of age followed for 10 years, the risk for the development of cholelithiasis was largest in those subjects in the age range 55–62 years, and the incidence of onset in females was more than twice as large as in males in any age range, and increased with age [58].

Obesity

Patients with cholelithiasis are more likely to be obese than those without [58], and cholelithiasis is a major comorbidity of obesity. The proportion of cholelithiasis and cholecystitis in the obese aged 37–60 years (female BMI > 34 [(weight kg)/(height m)^2], and male BMI > 38) was significantly higher than that in the non-obese (cholelithiasis: 5.8 vs. 1.5 %, odds ratio [OR] = 4.9; cholecystitis: 0.8 vs. 3.4 %, OR = 5.2) [59].

Role of pregnancy, fecundity, and fertility

No evidence exists to suggest an association between pregnancy/fecundity and the onset of acute cholangitis/cholecystitis.

The risk for cholecystectomy due to gallbladder diseases in middle-aged females (50–64 years of age) increased with the frequency of delivery and decreased in proportion to the duration of lactation [60]. Cholelithiasis accounted

Table 3 Percentage causes of acute cholangitis

References	Years	Setting	N	Causes				
				Gallbladder stones (%)	Benign stenosis (%)	Malignant stenosis (%)	Sclerosing cholangitis (%)	Others/ unknown (%)
Gigot [39]	1963–1983	University Paris	412	48	28	11	1.5	–
Saharia and Cameron [40]	1952–1974	Johns Hopkins Hospital, USA	76	70	13	17	0	–
Pitt and Couse [41]	1976–1978	Johns Hopkins Hospital, USA	40	70	18	10	3	–
Pitt and Couse [41]	1983–1985	Johns Hopkins Hospital, USA	48	32	14	30	24	–
Thompson [42]	1986–1989	Johns Hopkins Hospital, USA	96	28	12	57	3	–
Basoli [43]	1960–1985	University of Rome	80	69	16	13	0	4
Daida [44]	1979	Questionnaire throughout Japan	472	56	5	36	–	3
Salek [45]	2000–2005	Long Island Jewish Medical Center, USA	108	68	4	24	3	1

Table 4 Etiological mechanism of gallbladder diseases

Etiological mechanism	Drug/treatment
Direct chemical toxicity	Hepatic artery infusion
Promoted 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)
Promoted precipitation of calcium salt in bile	Ceftriaxone
Altered mobility of the gallbladder	Octreotide
	Narcoid
	Anticholinergic drugs
Promoted hemolysis	Dapson
Immunological mechanism	Antimicrobial drugs (erythromycin, ampicillin)
	Immunotherapy

Review by Michielsen et al. [62]

Drugs as etiological agents

for more than 90 % of the causes of cholelithiasis in pregnancy and cholelithiasis was the most frequently encountered surgical disease next to appendicitis [61]. Gallstones were detected by routine ultrasound imaging in 3.5 % of pregnant women, although it is not known whether or not pregnancy is associated with an increased risk of cholangitis [61].

According to a review by Michielsen et al., drugs promoting the generation of gallbladder stones were indirectly associated with a risk of acute cholecystitis [62]. A developmental mechanism of drug-associated gallbladder diseases in that review is presented in Table 4.

Statins, which are drugs for hyperlipidemia, may decrease the risk for cholecystectomy due to gallbladder stones [63–66]. There are also reports suggesting that thiazide was involved in the increased risk for cholecystectomy due to acute cholecystitis/gallbladder diseases [67–69], although there is a report that failed to detect an association [70]. Transcatheter hepatic arterial chemotherapy has been indicated to potentially induce chemical cholecystitis due to direct toxicity [62, 71]. The relative risk for the onset of cholecystitis or cholecystectomy due to hormone replacement therapy was two-fold larger [72, 73].

AIDS as a risk factor

Typical gallbladder diseases in AIDS patients are AIDS cholangiopathy and acute acalculous cholecystitis [74]. The former showed higher frequency similar to sclerosing cholangititis while the latter showed relatively low frequency. Abdominal operations in AIDS patients have found that the most frequently encountered causative disease was acute cholecystitis [75].

AIDS cholangiopathy is frequently observed in middle-aged patients (mean age 37 years; 21–59) with a mean 15 ± 2.2 month history of AIDS, and 90 % of chief complaints occur in the right upper quadrant abdomen. Biochemical examination demonstrates a marked elevation in the level of alkaline phosphatase [74]. Abdominal ultrasound, computed tomography (CT) [74], magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) [76], CT [74], and MRI/MRCP [76] shows imaging (occasionally, beading) of stenosis/dilatation in the intra-/extrahepatic bile duct.

Acute acalculous cholecystitis in AIDS patients was characterized by young age, availability of oral intake, pain in the right upper quadrant abdomen, marked elevation in the level of alkaline phosphatase and a slight increase in the serum bilirubin level, and accompanying cytomegalovirus infection or cryptosporidium infection [74].

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 stones present in the gallbladder neck and cystic ducts [77]. Two types have been described: type I, which is a morbid condition with the bile duct compressed from the left by the stones present in the gallbladder neck and cystic ducts and pericholecystic inflammatory changes (Fig. 4a–c, Supplementary Fig. 1a–c); and type II, which is a morbid condition with biliobiliary
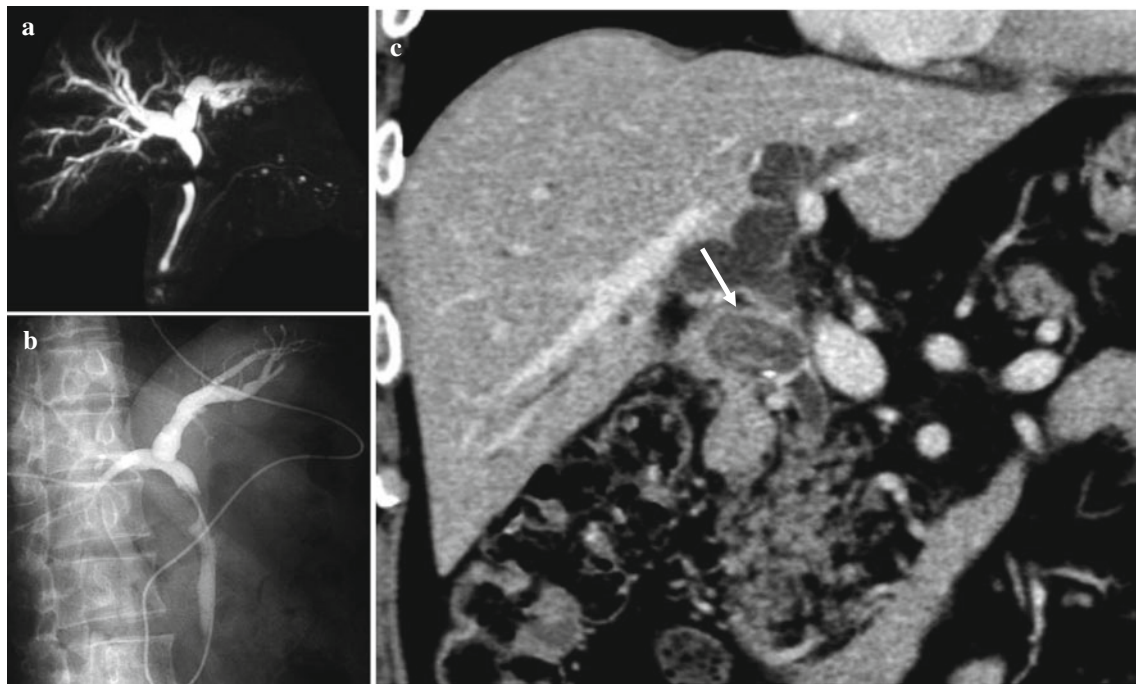
Fig. 4 Mirizzi syndrome. **a** MRCP showed the obstructed common hepatic duct but failed to visualize the gallbladder. **b** Cholangiography with an ENBD tube showed the stenosed common hepatic duct but failed to visualize the gallbladder. **c** Coronal images by contrast-enhanced CT clearly showing that stones impacted in the gallbladder duct have expanded the common hepatic duct, thereby inducing stenosis

Fig. 5 Lemmel syndrome. **a** Upper gastrointestinal endoscopy showing a diverticulum just above the papilla of Vater (*right arrow*). **b** ERCP demonstrating findings of extrinsic compression in the lower biliary tract (*right arrow*)
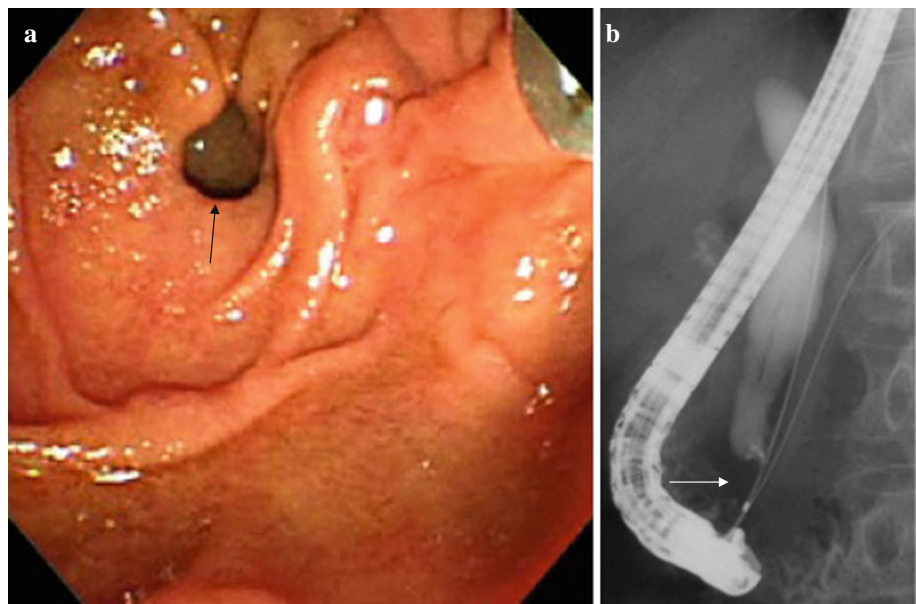
fistulation caused by pressure necrosis of the bile duct due to cholecystolithiasis [77]. Lemmel syndrome (Fig. 5a, b; Supplementary Fig. 2a, b) is a series of morbid conditions in which the duodenal parapapillary diverticulum compresses or displaces the opening of the bile duct or pancreatic duct and obstructs the passage of bile in the bile duct or hepatic duct, thereby causing cholestasis, jaundice, gallstone, cholangitis, and pancreatitis [78].

Prognosis

Mortality

Q8. What is the mortality rate of acute cholangitis/cholecystitis?

> Acute cholangitis; 2.7-10 %
> Acute cholecystitis; ~1 %

Acute cholangitis (Table 5)

It has been reported that the mortality rate of acute cholangitis was higher than 50 % before 1980, 10–30 % in 1981–1990s, and 2.7–10 % after 2000 [42, 45, 79–97]. Such differences in mortality rate are assumed to have arisen from differences in severity and diagnostic criteria for the accumulated cases.

Acute cholecystitis (Table 6)

The mortality rate in patients with acute cholecystitis has been reported to be 0–10 % [17, 21, 98–115]. According to reports after 2000, the mortality rate was less than 1 % [17, 105–115], and no marked difference according to eras and communities is present.

The mortality rate according to severity in TG07 was classified as mild (grade I) (1/161, 0.6 %), moderate (grade II) (0/60, 0 %), or severe (grade III) (3/14, 21.4 %). Overall, acute cholecystitis accounts for 1.7 % [21].

Table 5 Mortality rate of acute cholangitis

References	Period/year	Country	No. of cases	Mortality (%)
Andrew [79]	1957–1967	US	17[c]	64.71
Shimada [80]	1975–1981	Japan	42[b]	57.1
Csendes [81]	1980–1988	Chile	512	11.91
Himal [82]	1980–1989	Canada	61	18.03
Chijiiwa [83]	1980–1993	Japan	27[c]	11.11
Liu [84]	1982–1987	Taiwan	47[a]	27.66
Lai [85]	1984–1988	Hong Kong	86[b]	19.77
Thompson [42]	1984–1988	USA	127	3.94
Arima [86]	1984–1992	Japan	163	2.45
Kunisaki [87]	1984–1994	Japan	82	10.98
Tai [88]	1986–1987	Taiwan	225	6.67
Thompson [89]	1986–1989	USA	96	5.21
Sharma [90]	2000–2004	India	75 (7Fr-NBD)	2.7
			75 (7Fr stent)	2.7
Lee [91]	2001–2002[c]	Taiwan	112 (bacteremia)	13.4
Rahman [92]	2005	UK	122	10
Pang [93]	2003–2004	Hong Kong	171	6.4
Agarwal [94]	2001–2005	India	175	2.9
Tsujino [95]	1994–2005	Japan	343 (38[d])	5.3[d]
Rosing [96]	1995–2005	USA	117	8
Salek [45]	2000–2005	USA	108	24.1
Yeom [97]	2005–2007	Korea	181	0.5 (2[d])

[a] Only patients with shock

[b] Only severe cases

[c] Only patients with AOSC(Acute Obstructive Supprative Cholangitis)

[d] Only patients with Acute supprative cholangitis

Table 6 Mortality rate of acute cholecystitis

Author	Period/year	Country	Subjects	No. of cases	Mortality (%)
Meyer [98]	1958–1964	USA		245	4.49
Ranasohoff [99]	1960–1981	USA		298	3.36
Gagic [100]	1966–1971	USA		93	9.68
Girald [101]	1970–1986	Canada		1691	0.65
Addison [102]	1971–1990	UK		236	4.66
Bedirli [103]	1991–1994	Turkey		368	2.72
Gharaibeh [104]	1994–1999	Jordan		204	0
Russo MW [105]	2004	USA		262,411	0.6
Papi [106]	2004	Meta	Cholecystectomy	1009	0.9
			LC	246	0
Giger [107]	2005	System. rev.			0.26–0.6
Johansson [108]	2002–2004	Sweden	Cholecystectomy	35	0
			LC	35	0
Al Salamah [109]	1997–2002	Saudi Arabia	LC	311	0
Gurusamy [110]	2006	Meta	Early operation	223	0
			Delayed operation	228	0
Borzellino [111]	2008	Meta		1408	0
Lee [112]	2005–2006	USA		202	0
Csikesz [113]	2000–2005	USA	Cholecystectomy	152,202	3
			LC	859,747	0.4
Lee [21]	2007–2008	Taiwan		235	1.7
Gurusamy [114]	2010	Meta	Early operation	223	0
			Delayed operation	228	0
Sekimoto [115]	2004–2005	Japan	Total (operated cases)	738 (512)	0.9 (0.2)
	2006–2007	Japan	Total (operated cases)	3,858 (1,897)	1.9 (0.4)
	2008–2009	Japan	Total (operated cases)	8,026 (5,158)	2.9 (0.5)

Meta meta-analysis, *System. rev.* systematic review, *LC* laparoscopic cholecystectomy

Recurrence

Recurrence rate of acute cholecystitis

Q9. What is the recurrence rate for cases having undergone conservative treatment for acute cholecystitis?

> The recurrence rate for cases needed emergent hospitalization after having undergone conservative treatment or waiting for cholecystectomy was 19~36% (level B) and 22~47% for cases that do not undergo surgery after percutaneous gallbladder drainage.

Fundamentally, no recurrence has occurred for cases undergoing cholecystectomy for acute cholecystitis.

(1) Recurrence of acute cholecystitis for which remission was achieved with conservative treatment

According to randomized controlled trials comparing outcomes of cholecystectomy and follow-up after remission of acute cholecystitis, 36 % of the cases in the follow-up group subsequently required emergency hospitalization due to pain and gallstone-associated complications (acute cholecystitis, bile duct stones, acute pancreatitis) [116, 117] and 24–30 % required cholecystectomy [116–118].

On the other hand, the recurrence rate of acute cholecystitis cases waiting for cholecystectomy was 2.5–22 % [104, 116, 117, 119], and 19 % required emergency hospitalization [116, 117]. It has been reported that, of these recurrence cases, the recurrence of acute cholecystitis accounted for 2.5 % [104], 22 % [119], and gallbladder perforation 6 %, respectively [119].

(2) Recurrence of acute cholecystitis for which no cholecystectomy was carried out for some reason

Recurrence occurred in 22–47 % of acute cholecystitis cases undergoing follow-up without cholecystectomy subsequent to percutaneous gallbladder drainage [120–122].

Recurrence rate after treatment for gallbladder stones

Q10. What is the recurrence rate after endoscopic treatment for cholelithiasis?

> **Biliary events (cholelithiasis · biliary colic · cholangitis)；7~47%**
> **Acute cholecystitis with gallstone in-situ；5.6-22%**

Recurrence of complications in the biliary system

Following endoscopic sphincterectomy (EST), recurrence occurred in 7–47 % of cases with complications in the biliary tract system (cholelithiasis, biliary tract colic, cholangitis) within the 2.5–15-year follow-up period [123–129].

Recurrence of acute cholecystitis

It has been reported that the proportion of symptom appearance of acute cholecystitis (including cases in which symptoms have appeared) was 5.6–22 % [123, 125, 126, 128–130] when calculous gallbladder was left untreated after EST [123–126, 128–133] and 0–7 % for cases with acalculous gallbladder or after cholecystectomy [123–126, 130, 133] (Supplementary Table 2).

A risk factor for recurrence after endoscopic treatment for bile duct stones by means of endoscopic papillary balloon dilation (EPBD) is the occurrence of calculous gallbladder [134, 135]. Compared with treatment by means of EST, the incidence of acute cholecystitis a long time after treatment with EPBD is lower [136], although the recurrence rates of bile duct stones are the same (5.5 and 8.8 %) for both treatment methods [137].

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