TG13: Updated Tokyo Guidelines for the management of acute cholangitis and cholecystitis

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Abstract In 2007, the Tokyo Guidelines for the management of acute cholangitis and cholecystitis (TG07) were first published in the Journal of Hepato-Biliary-Pancreatic Surgery. The fundamental policy of TG07 was to achieve the objectives of TG07 through the development of consensus among specialists in this field throughout the world. Considering such a situation, validation and feedback from the clinicians’ viewpoints were indispensable. What had been pointed out from clinical practice was the low diagnostic sensitivity of TG07 for acute cholangitis and the presence of divergence between severity assessment and clinical judgment for acute cholangitis. In June 2010, we set up the Tokyo Guidelines Revision Committee for the revision of TG07 (TGRC) and started the validation of TG07. We also set up new diagnostic criteria and severity assessment criteria by retrospectively analyzing cases of acute cholangitis and cholecystitis, including cases of non-inflammatory biliary disease, collected from multiple institutions. TGRC held meetings a total of 35 times as well as international email exchanges with co-authors abroad. On June 9 and September 6, 2011, and on April 11, 2012.
2012, we held three International Meetings for the Clinical Assessment and Revision of Tokyo Guidelines. Through these meetings, the final draft of the updated Tokyo Guidelines (TG13) was prepared on the basis of the evidence from retrospective multi-center analyses. To be specific, discussion took place involving the revised new diagnostic criteria, and the new severity assessment criteria, new flowcharts of the management of acute cholangitis and cholecystitis, recommended medical care for which new evidence had been added, new recommendations for gallbladder drainage and antimicrobial therapy, and the role of surgical intervention. Management bundles for acute cholangitis and cholecystitis were introduced for effective dissemination with the level of evidence and the grade of recommendations. GRADE systems were utilized to provide the level of evidence and the grade of recommendations. TG13 improved the diagnostic sensitivity for acute cholangitis and cholecystitis, and presented criteria with extremely low false positive rates adapted for clinical practice. Furthermore, severity assessment criteria adapted for clinical use, flowcharts, and many new diagnostic and therapeutic modalities were presented. The bundles for the management of acute cholangitis and cholecystitis are presented in a separate section in TG13.


**Keywords**  Acute cholangitis · Acute cholecystitis · Charcot’s triad · Biliary infection · GRADE

**Background before Tokyo Guidelines 2007**

Acute cholangitis and cholecystitis require appropriate treatment in the acute phase. Severe acute cholangitis may result in early death if no appropriate medical care is provided in the acute phase. Before the publication of the Tokyo Guidelines for the management of acute cholangitis and cholecystitis (TG07) in January 2007 [1], there were no practical guidelines throughout the world primarily targeting acute cholangitis and cholecystitis.

TG07 had substantial influence on medical care for biliary infections throughout the world in that they clearly defined the diagnostic criteria and severity assessment criteria for acute cholangitis and cholecystitis, the definition of which had until then been ambiguous. TG07 has provided international standards for diagnostic and severity assessment criteria. This has enabled the comparison and integration of multiple studies (i.e., meta-analysis or systematic reviews).

TG07 was initially developed through the following processes. An international consensus meeting was held in Tokyo on April 1 and 2, 2006. A total of 29 experts from

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22 countries and Japanese experts in this field attended the meeting. To obtain consensus, a voting system was used. As the final product of this international consensus meeting, TG07 [2] was published in 2007.

The process of preparation was by no means easy. TG07 was the world’s first clinical practice guidelines on the management of acute cholangitis and cholecystitis. There were many obstacles to overcome. The preparation of TG07 started according to the principle of evidence-based medicine. However, due to the absence of diagnostic criteria and severity assessment criteria, studies available at that time were very few in number, and even if there was extracted evidence, the criteria lacked unity and the contents were often ambiguous. Furthermore, items to be discussed included diagnostic methods and clinical decision-making such as the selection of antimicrobial agents and their biliary penetration, the route and timing of biliary drainage, the timing of surgical intervention, and healthcare-associated (e.g., postoperative) cholangitis and cholecystitis. It took an enormously long time to cover the overall guidelines.

Citation analysis 2007–2011 of TG07

TG07 has been cited widely since its publication. The number of papers citing TG07 [1, 3–5] has been increasing every year [6] and has reached approximately 209 treatises. Those treatises have been cited in textbooks of surgery, internal medicine, and guidelines of abdominal infections [7–9]. The significance of this is that TG07 has had substantial influence on medical education and has become disseminated throughout the world as a global standard.

The results of the survey that examined the number of citations of TG07 until December 2011 show that the total number of citations of TG07 was 209 in 2009 (Table 1). The number of citations occurring each year since 2007 is presented in Fig. 1.

The number of journals that cited TG07 was 77. Figure 2 provides a breakdown of the fields of the journals that cited TG07.

There were 112 treatises that had been cited from TG07. Figure 3 provides a breakdown of the residential areas of the authors. Table 2 shows the types of articles which cited TG07. Of the 76 original treatises, 20 (26.3%) were cited in method sections (Fig. 4). The citation of original treatises in method sections has been on a rapid increase since 2011 (Fig. 5). Of the treatises cited in the method sections, studies had been conducted in 17 titles concerning diagnostic criteria and/or severity assessment criteria (Fig. 4). In summary, TG07 has been cited in journals in various fields throughout the world, although only 5 years’ citations were totaled.

**Need for revision of TG07**

1. The development of evidence-based guidelines, clinical practice and assessment

The publication of TG07 enabled the presentation of the first international diagnostic criteria and severity assessment...
criteria [1, 3–6] and, at the same time, the presentation of those criteria improved the quality of medical care
throughout the world, and the usefulness of TG07 has
come to be a target of appraisal from clinical viewpoints [10,
11]. TG07 should have been prepared primarily on the
basis of evidence. However, due to the paucity of evidence,
it was completed through combining “best available evi-
dence” and the worldwide knowledge cultivated at the
international consensus meeting. Therefore, a test by cli-
nicians for its usefulness is indispensable. TG07 has now
reached the stage when it can be further improved on the
basis of evidence and consensus as well as feedback from
clinical practice.

In general, following the publication of clinical practice
guidelines, new findings are reported concerning diagnosis
and therapeutic methods. Therefore clinical practice
guidelines require regular update and revision [12]. In view
of these circumstances, an evidence-based revision process
is also required for TG07. After its publication, an
appraisal from clinicians has been taking place concerning
dissemination/use and the results are being made good use
of for future revision (Fig. 6).

2. Validity of TG07

Given the critical appraisal of TG07, there are problems
in applying it in clinical settings. First, the sensitivity of
acute cholangitis is low. Second, there are impractical
aspects in the severity assessment criteria for moderate
acute cholangitis such as deciding the timing of biliary
drainage. There were discordances between clinical
judgement by clinicians and the level of severity utilizing
TG07 severity assessment criteria.

Process of the development of Tokyo Guidelines 2013
(TG13)

1. The First International Meeting for the development of
TG13

On June 9, 2011, the first International Meeting for
Clinical Assessment and Revision of the Tokyo Guidelines
was held. In this meeting, it was made clear that: (1) TG07
should be updated due to the presence of divergence
between TG07 and real clinical settings; (2) the validity of
the diagnostic criteria for acute cholangitis was to be
investigated on the basis of retrospective analysis of
patients with acute cholangitis collected from multiple
institutions; (3) there was divergence between severity
assessment and clinical judgement for acute cholangitis.

2. The Second International Meeting for the develop-
ment of TG13

On September 6, 2011, the Second International Meet-
ing for Clinical Assessment and Revision of the Tokyo
Guidelines was held. At the meeting, the overall action
plans for the new guidelines were determined with the draft
revision of the TG07 and the newly introduced Grades of
Recommendation, Assessment, Development and Evaluation

Table 2 Types of articles citing TG07

<table>
<thead>
<tr>
<th>Types of articles</th>
<th>No. of articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original article</td>
<td>76 (62.3 %)</td>
</tr>
<tr>
<td>Review</td>
<td>20 (16.4 %)</td>
</tr>
<tr>
<td>Case report</td>
<td>11 (9.0 %)</td>
</tr>
<tr>
<td>Guideline</td>
<td>7 (5.7 %)</td>
</tr>
<tr>
<td>Others</td>
<td>8 (6.6 %)</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
</tr>
</tbody>
</table>

Fig. 4 Section where cited in original articles (n = 76)

Fig. 5 Annual number of original articles citing papers in TG07

Fig. 6 Evidence–practice cycle
GRADE systems to provide the levels of evidence and grade of recommendations. In this meeting, antimicrobial therapy was mainly discussed. Using the two international meetings mentioned above as a basis, the revision work of TG07 started in 2011.

3. The validation study for acute cholangitis was presented in Kiriyama et al.’s paper [13].

4. The clinical study for Charcot’s triad was also described in Kiriyama et al.’s paper [13].

5. The validation study for acute cholecystitis was presented in Yokoe et al.’s paper [14].

6. Third International Meeting for the development of TG13

On April 11, 2012, the Third International Meeting for the Clinical Assessment and Revision of Tokyo Guidelines was held. In this meeting, the final draft of the updated Tokyo Guidelines was prepared on the basis of the evidence from the validation studies of TG07. To begin with, a discussion took place involving the updated new diagnostic criteria for which sensitivity and specificity had been improved, the new severity assessment criteria adapted for practical medical care, new flowcharts prepared for reducing divergence between evidence and clinical care, recommended medical care to which new evidence had been added, the new idea of gallbladder drainage and biliary drainage methods in clinical use, antimicrobial therapy, and the role of surgical intervention.

The concept and methodology of management bundles was introduced and discussed as tools for the effective dissemination and implementation of clinical practice guidelines by utilizing the GRADE systems for evidence assessment, and the concept of the grade of recommendation. As the results of the Third International Meeting for the Clinical Assessment and Revision of Tokyo Guidelines, the final draft was prepared through an international email conference with overseas co-authors. Thus TG13 was formulated.

The GRADE systems

The assessment of the evidence and the grading of recommendations in TG13 are based on the GRADE systems reported in 2004 and 2008 by the working team for the GRADE [15–17]. The assessment of the quality of evidence and the strength of recommendation are shown in Figs. 7 and 8, respectively.

In the assessment of the quality of evidence, the level of evidence is classified as “high” (level A), “moderate” (level B), “low” (level C), or “very low” (level D). A randomized trial is, in general, classified as having high-level evidence. However, due to limitations in each study, the quality of the study was re-assessed based on the limitations and the body of evidence was re-classified as “moderate” evidence. Observational studies (a non-randomized study, a cohort study, or a case–control study) are classified as having low-level evidence in general. The body of evidence may be upgraded to “high level” if it has significant influences in clinical practice. Case series or case reports are classified as having very low evidence, in general. It is extremely rare that the body of evidence is re-classified to a higher level. However, reports of cases of deaths due to complications or cases of significant side effects may be considered as a higher level.

The strength of recommendations was classified as “high (strong)” (recommendation 1) and “low (weak)” (recommendation 2). Four factors that determine the strength of recommendations are: (1) the quality of evidence; (2) sense of value and patient’s preference (less burden on staff members and patients); (3) net profits and cost/source (cost saving); and (4) benefits and harm burden (benefits and risks). The general decision was made by taking into account these four factors. Strong and weak recommendations were then determined by the Tokyo Guidelines Revision Committee. A strong recommendation suggests that desirable effects clearly exceed undesirable effects and is applied to recommendations on which more than 70 % of the members of the Tokyo Guidelines Revision Committee have agreed. The use of “We recommend …” has been adopted for the style of the expression. A weak recommendation shows that desirable effects probably exceed undesirable effects and the use of “We suggest …” has been adopted.

The recommendation 1 level A (strong recommendation; evidence level high), 1B, 1C, 1D, 2A, 2B, 2C, and 2D (weak recommendation; evidence level very low) are shown at the end of recommendations. However, cases with strong recommendation (recommendation 1) may include those cases for which “to perform …” is strongly recommended and those for which “not to perform …” is strongly recommended.

Introduction of bundles for the management of acute cholangitis and cholecystitis

We presented and discussed the concept and the method of management bundles in TG13. Concrete objectives and anticipated effects of the bundles are as follows: (1) to achieve improved prognosis by using bundles of treatment methods with evidence presented in the guidelines (TG13); (2) to achieve higher compliance and remove barriers among institutions by presenting a list of guidelines in the form of bundles; (3) to carry out a survey involving compliance with the items of the medical care recommended by
the guidelines and to provide guidelines for conducting a survey concerning changes in medical care before and after publication of TG13.

Summary

This paper presents the background of TG07, its clinical impact since publication, the clinical appraisal emerging from clinical research, the process of revision of TG07, and the development of TG13. The guidelines need continuous evaluation and revision. TG13 has been developed to improve the quality of medical care for patients with acute cholangitis and cholecystitis. The guidelines should be widely utilized and prospective clinical studies are needed for further improvement in the near future.

Conflict of interest None.


GUIDELINE

TG13: Updated Tokyo Guidelines for acute cholangitis and acute cholecystitis

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).


Keywords Terminology · Etiology · Epidemiology · Acute cholangitis · Acute cholecystitis

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 cholecystitis 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, 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](image-url)
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).

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?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Asymptomatic, mild symptom - patients</th>
<th>Acute cholangitis</th>
<th>Acute cholecystitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>~40 %/5-10 years</td>
<td>0.3 – 1.6 %</td>
<td>3.8 – 12%</td>
</tr>
<tr>
<td>Annual proportion</td>
<td>1-3%/year</td>
<td></td>
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</table>

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.
millions 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% per 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 (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

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholelithiasis</td>
<td></td>
</tr>
<tr>
<td>Benign biliarystricture</td>
<td></td>
</tr>
<tr>
<td>Congenital factors</td>
<td></td>
</tr>
<tr>
<td>Post-operative factors</td>
<td>(damaged bile duct, strictured choledojejunostomy, etc.)</td>
</tr>
<tr>
<td>Inflammatory factors</td>
<td>(oriental cholangitis, etc.)</td>
</tr>
<tr>
<td>Malignant occlusion</td>
<td></td>
</tr>
<tr>
<td>Bile duct tumor</td>
<td></td>
</tr>
<tr>
<td>Gallbladder tumor</td>
<td></td>
</tr>
<tr>
<td>Ampullary tumor</td>
<td></td>
</tr>
<tr>
<td>Pancreatic tumor</td>
<td></td>
</tr>
<tr>
<td>Duodenal tumor</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Entry of parasites into the bile ducts</td>
<td></td>
</tr>
<tr>
<td>External pressure</td>
<td></td>
</tr>
<tr>
<td>Fibrosis of the papilla</td>
<td></td>
</tr>
<tr>
<td>Duodenal diverticulum</td>
<td></td>
</tr>
<tr>
<td>Blood clot</td>
<td></td>
</tr>
<tr>
<td>Sump syndrome after biliary enteric anastomosis</td>
<td></td>
</tr>
<tr>
<td>Iatrogenic factors</td>
<td></td>
</tr>
</tbody>
</table>

Reviewed by Kimura et al. [1]
Acute cholecystitis

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

**Etiology**
- Cystic duct obstruction (Gallstones 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

<table>
<thead>
<tr>
<th>References</th>
<th>Years</th>
<th>Setting</th>
<th>N</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saharia and Cameron [40]</td>
<td>1952–1974</td>
<td>Johns Hopkins Hospital, USA</td>
<td>76</td>
<td>Benign stenosis (%)</td>
</tr>
<tr>
<td>Pitt and Couse [41]</td>
<td>1976–1978</td>
<td>Johns Hopkins Hospital, USA</td>
<td>40</td>
<td>Malignant stenosis (%)</td>
</tr>
<tr>
<td>Pitt and Couse [41]</td>
<td>1983–1985</td>
<td>Johns Hopkins Hospital, USA</td>
<td>48</td>
<td>Sclerosing cholangitis (%)</td>
</tr>
<tr>
<td>Thompson [42]</td>
<td>1986–1989</td>
<td>Johns Hopkins Hospital, USA</td>
<td>96</td>
<td>Others/unknown (%)</td>
</tr>
<tr>
<td>Daida [44]</td>
<td>1979</td>
<td>Questionnaire throughout Japan</td>
<td>472</td>
<td></td>
</tr>
<tr>
<td>Salek [45]</td>
<td>2000–2005</td>
<td>Long Island Jewish Medical Center, USA</td>
<td>108</td>
<td></td>
</tr>
</tbody>
</table>
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].

**Drugs as etiological agents**

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.

**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 cholangitis 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

**Table 4 Etiological mechanism of gallbladder diseases**

<table>
<thead>
<tr>
<th>Etiological mechanism</th>
<th>Drug/treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct chemical toxicity</td>
<td>Hepatic artery infusion</td>
</tr>
<tr>
<td>Promoted stone formation by bile</td>
<td></td>
</tr>
<tr>
<td>Inhibition of ACAT activity</td>
<td>Progesterone, fibrate</td>
</tr>
<tr>
<td>Increased hepatic lipoprotein receptors</td>
<td></td>
</tr>
<tr>
<td>Induction of acute cholecystitis in patients with cholelithiasis</td>
<td>Thiazides (unconfirmed)</td>
</tr>
<tr>
<td>Promoted precipitation of calcium salt in bile</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>Altered mobility of the gallbladder</td>
<td>Octreotide</td>
</tr>
<tr>
<td>Promoted hemolysis</td>
<td>Dapson</td>
</tr>
<tr>
<td>Immunological mechanism</td>
<td>Antimicrobial drugs (erythromycin, ampicillin)</td>
</tr>
</tbody>
</table>

Review by Michielsen et al. [62]
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

<table>
<thead>
<tr>
<th>References</th>
<th>Period/year</th>
<th>Country</th>
<th>No. of cases</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrew [79]</td>
<td>1957–1967</td>
<td>US</td>
<td>17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>64.71</td>
</tr>
<tr>
<td>Shimada [80]</td>
<td>1975–1981</td>
<td>Japan</td>
<td>42&lt;sup&gt;b&lt;/sup&gt;</td>
<td>57.1</td>
</tr>
<tr>
<td>Csendes [81]</td>
<td>1980–1988</td>
<td>Chile</td>
<td>512</td>
<td>11.91</td>
</tr>
<tr>
<td>Himal [82]</td>
<td>1980–1989</td>
<td>Canada</td>
<td>61</td>
<td>18.03</td>
</tr>
<tr>
<td>Chijiwa [83]</td>
<td>1980–1993</td>
<td>Japan</td>
<td>27&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11.11</td>
</tr>
<tr>
<td>Liu [84]</td>
<td>1982–1987</td>
<td>Taiwan</td>
<td>47&lt;sup&gt;a&lt;/sup&gt;</td>
<td>27.66</td>
</tr>
<tr>
<td>Lai [85]</td>
<td>1984–1988</td>
<td>Hong Kong</td>
<td>86&lt;sup&gt;b&lt;/sup&gt;</td>
<td>19.77</td>
</tr>
<tr>
<td>Tai [88]</td>
<td>1986–1987</td>
<td>Taiwan</td>
<td>225</td>
<td>6.67</td>
</tr>
<tr>
<td>Thompson [89]</td>
<td>1986–1989</td>
<td>USA</td>
<td>96</td>
<td>5.21</td>
</tr>
<tr>
<td>Sharma [90]</td>
<td>2000–2004</td>
<td>India</td>
<td>75 (7Fr-NBD)</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75 (7Fr stent)</td>
<td>2.7</td>
</tr>
<tr>
<td>Lee [91]</td>
<td>2001–2002&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Taiwan</td>
<td>112 (bacteremia)</td>
<td>13.4</td>
</tr>
<tr>
<td>Rahman [92]</td>
<td>2005</td>
<td>UK</td>
<td>122</td>
<td>10</td>
</tr>
<tr>
<td>Pang [93]</td>
<td>2003–2004</td>
<td>Hong Kong</td>
<td>171</td>
<td>6.4</td>
</tr>
<tr>
<td>Agarwal [94]</td>
<td>2001–2005</td>
<td>India</td>
<td>175</td>
<td>2.9</td>
</tr>
<tr>
<td>Tsujino [95]</td>
<td>1994–2005</td>
<td>Japan</td>
<td>343 (38&lt;sup&gt;g&lt;/sup&gt;)</td>
<td>5.3&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Yoon [97]</td>
<td>2005–2007</td>
<td>Korea</td>
<td>181</td>
<td>0.5 (2&lt;sup&gt;h&lt;/sup&gt;)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Only patients with shock
<sup>b</sup> Only severe cases
<sup>c</sup> Only patients with AOSC (Acute Obstructive Suppurative Cholangitis)
<sup>d</sup> Only patients with Acute suppurative cholangitis
Recurrence

**Recurrence rate of acute cholecystitis**

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

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].

---

<table>
<thead>
<tr>
<th>Author</th>
<th>Period/year</th>
<th>Country</th>
<th>Subjects</th>
<th>No. of cases</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranasohoff [99]</td>
<td>1960–1981</td>
<td>USA</td>
<td></td>
<td>298</td>
<td>3.36</td>
</tr>
<tr>
<td>Gagic [100]</td>
<td>1966–1971</td>
<td>USA</td>
<td></td>
<td>93</td>
<td>9.68</td>
</tr>
<tr>
<td>Girald [101]</td>
<td>1970–1986</td>
<td>Canada</td>
<td></td>
<td>1691</td>
<td>0.65</td>
</tr>
<tr>
<td>Bedirli [103]</td>
<td>1991–1994</td>
<td>Turkey</td>
<td></td>
<td>368</td>
<td>2.72</td>
</tr>
<tr>
<td>Gharaibeh [104]</td>
<td>1994–1999</td>
<td>Jordan</td>
<td></td>
<td>204</td>
<td>0</td>
</tr>
<tr>
<td>Russo MW [105]</td>
<td>2004</td>
<td>USA</td>
<td></td>
<td>262,411</td>
<td>0.6</td>
</tr>
<tr>
<td>Papi [106]</td>
<td>2004</td>
<td>Meta</td>
<td>Cholecystectomy</td>
<td>1009</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LC</td>
<td>246</td>
<td>0</td>
</tr>
<tr>
<td>Giger [107]</td>
<td>2005</td>
<td>System. rev.</td>
<td></td>
<td></td>
<td>0.26–0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LC</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Al Salamah [109]</td>
<td>1997–2002</td>
<td>Saudi Arabia</td>
<td>LC</td>
<td>311</td>
<td>0</td>
</tr>
<tr>
<td>Gurusamy [110]</td>
<td>2006</td>
<td>Meta</td>
<td>Early operation</td>
<td>223</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Delayed operation</td>
<td>228</td>
<td>0</td>
</tr>
<tr>
<td>Borzellino [111]</td>
<td>2008</td>
<td>Meta</td>
<td></td>
<td>1408</td>
<td>0</td>
</tr>
<tr>
<td>Lee [112]</td>
<td>2005–2006</td>
<td>USA</td>
<td></td>
<td>202</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LC</td>
<td>859,747</td>
<td>0.4</td>
</tr>
<tr>
<td>Gurusamy [114]</td>
<td>2010</td>
<td>Meta</td>
<td>Early operation</td>
<td>223</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Delayed operation</td>
<td>228</td>
<td>0</td>
</tr>
<tr>
<td>Sekimoto [115]</td>
<td>2004–2005</td>
<td>Japan</td>
<td>Total (operated cases)</td>
<td>738 (512)</td>
<td>0.9 (0.2)</td>
</tr>
<tr>
<td></td>
<td>2006–2007</td>
<td>Japan</td>
<td>Total (operated cases)</td>
<td>3,858 (1,897)</td>
<td>1.9 (0.4)</td>
</tr>
<tr>
<td></td>
<td>2008–2009</td>
<td>Japan</td>
<td>Total (operated cases)</td>
<td>8,026 (5,158)</td>
<td>2.9 (0.5)</td>
</tr>
</tbody>
</table>

Meta meta-analysis, System. rev. systematic review, LC laparoscopic cholecystectomy
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 rate after treatment for gallbladder stones

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].

Acknowledgments

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Conflict of interest

None.

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TG13 guidelines for diagnosis and severity grading of acute cholangitis (with videos)

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Abstract Since the publication of the Tokyo Guidelines for the management of acute cholangitis and cholecystitis (TG07), diagnostic criteria and severity assessment criteria for acute cholangitis have been presented and extensively used as the primary standard all over the world. However, it has been found that there are crucial limitations in these criteria. The diagnostic criteria of TG07 do not have enough sensitivity and specificity, and its severity assessment criteria are unsuitable for clinical use. A working team for the revision of TG07 was organized in June, 2010, and these criteria have been updated through clinical implementation and its assessment by means of multi-center analysis. The diagnostic criteria of acute cholangitis have been revised as criteria to establish the diagnosis where cholestasis and inflammation demonstrated by clinical signs or blood test in addition to biliary manifestations demonstrated by imaging are present. The diagnostic criteria of the updated Tokyo Guidelines (TG13) have high sensitivity (87.6 %) and high specificity (77.7 %). TG13 has better diagnostic capacity than TG07. Severity assessment is classified as follows: Grade III: associated with organ failure; Grade II: early biliary drainage should...
be conducted; Grade I: others. As for the severity assessment criteria of TG07, separating Grade II and Grade I at the time of diagnosis was impossible, so they were unsuitable for clinical practice. Therefore, the severity assessment criteria of TG13 have been revised so as not to lose the timing of biliary drainage or treatment for etiology. Based on evidence, five predictive factors for poor prognosis in acute cholangitis—hyperbilirubinemia, high fever, leukocytosis, elderly patient and hypoalbuminemia—have been extracted. Grade II can be diagnosed if two of these five factors are present.


Keywords  
Acute cholangitis  
Diagnostic criteria  
Severity assessment  
Diagnostic imaging guidelines

Introduction

Patients with acute cholangitis are at risk of developing severe and potentially lethal infections such as sepsis unless appropriate medical care is provided promptly. As a therapeutic procedure for severe cases or to prevent increased severity, decompression of the biliary tract (i.e., biliary tract drainage) is necessary. Recent advances in and diffusion of endoscopic biliary tract drainage along with the administration of antimicrobial agents have contributed to the decrease in the number of deaths due to acute cholangitis. However, it remains a life-threatening disease if the timing of biliary tract drainage has been missed. Therefore, immediate and precise judgment of severity is of the utmost importance.

Since Charcot reported a patient with severe acute cholangitis as a case of “hepatic fever” in 1877, Charcot’s triad has been widely used as one of the most important diagnostic criteria [1–5]. However, Charcot’s triad has extremely low sensitivity despite its high specificity. In 2006, we conducted a systematic review of references and sponsored the International Consensus Meeting of Tokyo Guidelines, which resulted in the introduction of new diagnostic criteria and severity assessment criteria in the Tokyo Guidelines for the management of acute cholangitis and cholecystitis (TG07) [6].

Diagnostic criteria and severity assessment criteria should be reconsidered and updated according to their implementation in clinical settings and their assessment. In TG07, there are impractical aspects and discrepancies between the diagnostic criteria and severity assessment criteria of acute cholangitis and the actual clinical settings [7]. Therefore, in order to make the updated Tokyo Guidelines (TG13), the working team carried out a retrospective observational study in multiple tertiary care centers in Japan. This study found limitations in the diagnostic criteria and severity assessment criteria of TG07. The problems which were made clear by the implementation and assessment of TG07 were then corrected, and new updated diagnostic criteria and severity assessment criteria were presented [8]. TG13 provides more accurate and
reliable diagnostic criteria and severity assessment criteria for acute cholangitis to enable us to perform biliary drainage or other procedures without delay as compared with TG07.

**Diagnostic criteria for acute cholangitis**

**Background**

**Charcot’s triad**

**Q1. What is the role of Charcot’s triad in the diagnostic criteria for acute cholangitis?**

Charcot’s triad shows very high specificity. The presence of any one sign of Charcot’s triad strongly suggests the presence of acute cholangitis. However, due to the low sensitivity, it is not applicable in using as diagnosis criteria for acute cholangitis (level B).

A diagnosis of acute cholangitis has traditionally been made according to the presence of Charcot’s triad, that is, a clinical sign. Charcot’s triad has high specificity [9] but low sensitivity. According to several reports, cases presenting all the symptoms of Charcot’s triad accounted for 26.4–72 % [2, 3, 8–14].

The previous definition of acute cholangitis was not clear and varied in different references. Therefore, in the analysis of cases of biliary tract diseases collected from multiple facilities, we defined the “gold standard” for acute cholangitis, that one of the three following conditions was present: (1) Purulent bile was observed. (2) Clinical remission followed bile duct drainage. (3) Remission was achieved by antibacterial therapy alone, in patients in whom the only site of infection was the biliary tree. So it showed low sensitivity (26.4 %) when Charcot’s triad was adopted as a diagnostic criterion for acute cholangitis. On the other hand, the specificity was very favorable (95.9 %), but it was positive (11.9 %) for acute cholecystitis. The presence of Charcot’s triad supports the diagnosis of acute cholangitis. However, judging from the low sensitivity, Charcot’s triad as a diagnostic criterion for acute cholangitis is doubtful [8].

**TG07 diagnostic criteria for acute cholangitis**

**Q2. How are the diagnostic criteria for acute cholangitis in TG07 appraised?**

Although the sensitivity has been improved compared with Charcot’s triad, TG07 have limitations and their validity is insufficient for using them to make a diagnosis of life-threatening acute cholangitis without a rapid clinical suspicion and appropriate treatment (level B).

As has already been mentioned, there were limitations in Charcot’s triad due to its low diagnostic sensitivity; however, there was no alternative diagnostic criterion. Under these circumstances, the International Consensus Meeting was held in Tokyo in 2006 so that an international
agreement could be reached on diagnostic criteria and severity assessment criteria. At that meeting, diagnostic criteria were presented combining blood tests and diagnostic imaging together with Charcot’s triad [15]. Diagnostic criteria were then established in TG07.

However, there has been a report showing that, even in TG07, the sensitivity is low (63.9 %) for making a definite diagnosis of acute cholangitis [7]. We carried out a multi-center analysis and found that the sensitivity was 82.6 % and the specificity was 79.8 % [8]. The diagnostic criteria for acute cholangitis in TG07 were found to be insufficient for making a diagnosis of life-threatening acute cholangitis without a rapid diagnosis and appropriate treatment.

Revision of TG07 diagnostic criteria for acute cholangitis

Due to the inappropriate combination of such items as clinical context and manifestations, laboratory data and imaging findings, TG07 failed to associate them with three types of morbid conditions of acute cholangitis. We then performed an analysis of each of the items of the diagnostic criteria in TG07, which can be classified as the following three morbidities: (1) fever and/or evidence of inflammatory response such as inflammation, (2) jaundice and abnormal liver function test results such as cholestasis, and (3) a history of biliary diseases, abnormal pain and biliary dilatation, or evidence of etiology such as biliary manifestations. It was considered that those cases meeting these 3 categories can be diagnosed as acute cholangitis. However, a history of biliary diseases and abdominal pain is not specific to biliary manifestations, thus making the differentiation from acute cholecystitis or acute hepatitis impossible. Consequently, abdominal pain and a history of biliary diseases were excluded. To make up for the reduced sensitivity due to the exclusion of abdominal pain, “suspected diagnosis” in which inflammatory findings are dispensable was added. By establishing “suspected diagnosis,” early biliary drainage or source control of infection among patients with acute cholangitis can be provided without waiting for the definitive diagnosis [8].

TG13 diagnostic criteria for acute cholangitis

The revised diagnostic criteria for acute cholangitis are shown in Table 1. The morbidity of acute cholangitis is associated with the occurrence of cholangiovenous and cholangiolymphatic reflux along with elevated pressure in the biliary ducts and bile infections due to bile duct obstruction induced by stones and tumors. TG13 Diagnostic Criteria of Acute Cholangitis are criteria to establish the diagnosis when cholestasis and inflammation based on clinical signs or blood test in addition to biliary manifestations based on imaging are present.

Q3. How are TG13 diagnostic criteria for acute cholangitis appraised?

TG13 diagnostic criteria for acute cholangitis is more accurate and reliable diagnostic capacity than TG07 (recommendation I, level B).

A multi-center analysis assessing TG13 found that the sensitivity was 91.8 % and the specificity was 77.7 %. TG13 showed similar specificity to TG07 but showed markedly increased sensitivity and further improvement in diagnostic ability (Table 2). The specificity of Charcot’s triad was the highest. The presence of Charcot’s triad strongly suggested the presence of acute vasculitis [8].

Systemic inflammation

Acute cholangitis is accompanied by the findings of systemic inflammation due to fever or an increased inflammatory response such as an increased white blood cell count and high levels of C-reactive protein (CRP). While an increase in the white blood cell count is observed in 82 %, a decrease may be observed in severe vasculitis [5].

Cholestasis

Many reports show that jaundice is observed in 60–70 % of cases of acute cholangitis (Table 2). A blood test shows an increase in the levels of ALP, γGTP, LAP and transaminases (AST, ALT). The threshold in liver function tests is particularly important in differentiating from acute cholecystitis when making a diagnosis of acute cholangitis according to the present diagnostic criteria. The thresholds of the tests needed to be established. However, the normal range of liver function tests differs from facility to facility. A fixed threshold is, therefore, not practical. From the results of multi-center analysis, it is appropriate and practical that the threshold is set at 1.5 times the normal upper limit for the liver function test [8].

Imaging findings

There were no direct imaging findings which showed evidence of bile infection. Recently, it has been reported that acute cholangitis can directly be depicted by computed tomography (CT) of the abdomen with contrast (Figs. 1, 2).

However, in clinical practice, imaging modalities usually support the diagnosis of acute cholangitis by showing indirect findings, which are biliary dilatation or evidence of
its etiology. A diagnosis of acute cholangitis requires that the presence of stones, tumors or stents inducing bile duct dilatation or cholangitis is confirmed with ultrasonography (US) of the abdomen (Supplementary Figures 1, 2, Supplementary Movie), CT of the abdomen with contrast (Figs. 1, 2; Supplementary Figure 3) and magnetic resonance cholangiopancreatography (MRCP) (Supplementary Figure 6).

Q4. Is it possible to diagnose acute cholangitis by computed tomography (CT) of the abdomen?

We suggested that dynamic CT of the abdomen with contrast enables making the diagnosis of acute cholangitis (recommendation 2, level D).

Radiological examinations such as ultrasonography, CT and magnetic resonance imaging (MRI) are carried out for evaluation of the site and cause of biliary obstruction and degree of biliary dilatation. However, CT of the abdomen with contrast has limitations in the diagnosis and evaluation of acute cholangitis [16]. Because helical CT is clinically available, the whole of the upper abdominal organs

Table 1  TG13 diagnostic criteria for acute cholangitis

<table>
<thead>
<tr>
<th>A. Systemic inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-1. Fever and/or shaking chills</td>
</tr>
<tr>
<td>A-2. Laboratory data: evidence of inflammatory response</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Cholestasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-1. Jaundice</td>
</tr>
<tr>
<td>B-2. Laboratory data: abnormal liver function tests</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-1. Biliary dilatation</td>
</tr>
<tr>
<td>C-2. Evidence of the etiology on imaging (stricture, stone, stent etc.)</td>
</tr>
</tbody>
</table>

Suspected diagnosis: One item in A + one item in either B or C
Definite diagnosis: One item in A, one item in B and one item in C

Note:
A-2: Abnormal white blood cell counts, increase of serum C-reactive protein levels, and other changes indicating inflammation
B-2: Increased serum ALP, GTP (GGT), AST and ALT levels.

Other factors which are helpful in diagnosis of acute cholangitis include abdominal pain [right upper quadrant (RUQ) or upper abdominal] and a history of biliary disease such as gallstones, previous biliary procedures, and placement of a biliary stent.

In acute hepatitis, marked systematic inflammatory response is observed infrequently. Virological and serological tests are required when differential diagnosis is difficult.

Thresholds

| A-1 | Fever | BT >38 °C |
| A-2 | Evidence of inflammatory response | WBC (×1000/μL) <4, or >10 |
|     |       | CRP (mg/dl) ≥1 |
| B-1 | Jaundice | T-Bil ≥2 (mg/dL) |
| B-2 | Abnormal liver function tests | ALP (IU) >1.5 × STD |
|     |       | GTP (IU) >1.5 × STD |
|     |       | AST (IU) >1.5 × STD |
|     |       | ALT (IU) >1.5 × STD |

Cited from the Ref. [8]

STD upper limit of normal value, ALP alkaline phosphatase, GTP (GGT) γ-glutamyltransferase, AST aspartate aminotransferase, ALT alanine aminotransferase

Table 2  Retrospective comparison of various diagnostic criteria of acute cholangitis in a multi-center study in Japan

<table>
<thead>
<tr>
<th>Charcot’s triad (%)</th>
<th>TG07 (%)</th>
<th>The first draft criteria (with abdominal pain and history of biliary disease) (%)</th>
<th>TG13 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity 26.4</td>
<td>82.6</td>
<td>95.1</td>
<td>91.8</td>
</tr>
<tr>
<td>Specificity 95.9</td>
<td>79.8</td>
<td>66.3</td>
<td>77.7</td>
</tr>
<tr>
<td>[Positive rate]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute cholecystitis  11.9</td>
<td>15.5</td>
<td>38.8</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Cited from Ref. [8]
Fig. 1 CT demonstrating acute cholangitis with gallstone and common bile duct stone (74-year-old female). Precontrast CT (a) shows gallstone (arrow) and common bile duct stone (arrowhead). The arterial phase of contrast-enhanced dynamic CT (b) shows diffuse inhomogeneous enhancement of the liver. In the equilibrium phase of dynamic CT (c), the inhomogeneous enhancement disappears.

Fig. 2 CT demonstrating acute cholangitis with gallstone and papillary tumor of the duodenum (77-year-old female). a, b Precontrast CT, c, d arterial phase of dynamic CT, e, f equilibrium phase. Precontrast CT shows gallstones (b arrow). Arterial phase of dynamic CT shows enhanced papillary tumor of the duodenum (d arrowhead). The liver parenchyma shows inhomogeneous enhancement surrounding the bile ducts, indicating acute cholangitis. In the equilibrium phase, inhomogeneous enhancement disappears.
can be assessed by contrast-enhanced dynamic CT. Pre-and postcontrast CT can depict biliary stones, pneumobilia, bile duct dilatation, bile duct wall thickening, and bile duct stenosis or occlusion. However, such CT findings do not necessarily suggest the presence of acute cholangitis.

Hepatic parenchymal changes seen at imaging in acute cholangitis are likely to be related to the extension of the inflammatory process into the periportal tissues [17–20]. In acute cholangitis, the inflammatory process of the peripheral bile duct spreading as far as the periportal areas (Glisson’s sheath) causes a decreased portal blood flow and an increased arterial blood flow. On the arterial phase of dynamic CT, inhomogeneous hepatic parenchymal enhancement (nodular, patchy, wedge-shaped or geographic) is frequently seen in patients with acute cholangitis [16, 17] (Figs. 1, 2). This inhomogeneous hepatic enhancement of contrast-enhanced dynamic CT appears in the arterial phase only, and disappears in the portal and equilibrium phases. Follow-up dynamic CT performed after treatment for acute cholangitis showed decreased or no inhomogeneous enhancement, according to the improvement of biliary inflammation (Supplementary Figure 4).

In conclusion, contrast-enhanced dynamic CT is recommended for making a prompt diagnosis of clinically suspected acute cholangitis.

Q5. Can CT make a diagnosis of the etiology and complications of acute cholangitis?

CT is suggested as the most effective imaging method for the diagnosis of etiology and complication of acute cholangitis (recommendation 2, level D).

CT scan is a useful imaging modality for exploring the etiology of acute cholangitis such as biliary stones (cholelithiasis, choledocholithiasis, hepatolithiasis) and pancreaticobiliary malignancies (extrahepatic bile duct carcinoma, gallbladder carcinoma, pancreatic head carcinoma). Because non-calcified biliary stones cannot be detected by CT, ultrasonography and/or MRI (MRCP) is also recommended (Supplementary Figure 5).

Hepatic abscesses sometimes occur in patients with acute cholangitis. It is important to differentiate abscesses from malignant hepatic tumors such as liver metastasis or intrahepatic cholangiocarcinoma. Characteristic imaging findings of hepatic abscesses have also been reported in dynamic CT as well as acute cholangitis [21–24] (Supplementary Figure 6). Hepatic abscess shows a double target sign with a transient segmental enhancement in the arterial phase of dynamic CT. The segmental enhancement disappears in the equilibrium phase. This transient segmental enhancement in dynamic CT reflects a decrease in segmental portal blood flow and an increase in compensatory hepatic arterial blood flow due to periportal inflammation within the Glisson’s sheath adjacent to the hepatic abscess [24, 25].

Q6. What are the indication and significance of MRI (MRCP) for acute cholangitis?

MRI (MRCP) is suggested for the etiologic diagnosis of acute cholangitis (recommendation 2, level D).

Magnetic resonance cholangiopancreatography (MRCP) has a high sensitivity for detecting biliary calculi and malignant biliary obstruction [25–27] (Supplementary Figure 7). Inhomogeneous enhancement in dynamic MRI as well as dynamic CT is also able to depict acute cholangitis [28].

Other factors which are helpful in diagnosis of acute cholangitis

A past history of gallbladder diseases is found in many reports of acute cholangitis [2, 3, 10–14], and it is referred to as ‘the past history of surgery for the diseases of the biliary system’, supposedly cholecystectomy for gallbladder stones in particular [3, 10–13].

The importance of ‘the past history of biliary diseases’ in a diagnosis of acute cholangitis was recognized at the International Consensus Meeting in 2006. The presence of bile stones and the placement of stents in the biliary tract were also considered to be contributing factors in making a diagnosis of acute cholangitis.

Abdominal pain is reported to be observed in 80 % or more cases (Table 3). However, it is not a symptom specific to cholangitis. It was excluded from the diagnostic criteria for acute cholangitis for the reason that its presence reduced the specificity and complicated the differentiation from acute cholecystitis [8].

Severity assessment criteria for acute cholangitis

Background

Patients with acute cholangitis may present with any severity ranging from self-limiting to severe and/or potentially life-threatening diseases. Most cases respond to initial medical treatment consisting of general supportive therapy and intravenous antimicrobial therapy.
It has been reported in the United States that approximately 70% of patients with acute cholangitis are able to achieve improvement with medical therapy alone [29]. Some cases do not respond to medical treatment and the clinical manifestations and laboratory data do not improve. Such cases may progress to sepsis with or without organ dysfunction and require appropriate management that includes intensive care, organ-supportive care, and urgent biliary drainage, in addition to medical treatment. There is also a report showing approximately a 10% mortality rate due to acute cholangitis despite the occurrence of responses to antimicrobial therapy and biliary drainage [30, 31].

**TG07 severity assessment criteria for acute cholangitis**

TG07 established the world’s first severity assessment criteria for acute cholangitis at the International Consensus Meeting in Tokyo in 2006 [6] and classified those conditions with organ dysfunction as ‘severe’ (Grade III), those showing no responses to the initial treatment as ‘moderate’ (Grade II), and those responding to the initial treatment as ‘mild’ (Grade I).

However, the use of TG07 severity assessment criteria in actual situations has shown that it is impossible to distinguish moderate cases (Grade II) and mild cases (Grade I) as soon as the initial diagnosis has been made. In TG07, Grades II and I were only assessed after observation of the treatment courses. In this treatment strategy, urgent biliary drainage can be indicated for cases assessed as severe, but provision of early biliary drainage is impossible. Acute cholangitis can progress rapidly to sepsis and disseminated intravascular coagulation (DIC) and the “observation strategy” in TG07 may induce increased severity during the initial treatment. In Japan, many cases (46.8%, 258 of 551 cases) of Grades II or I underwent urgent biliary drainage in the same manner as Grade III. In these cases, differentiation between Grade II and Grade I was impossible, because the definition of Grade II in TG07 was ambiguous [8].

**Revision of TG07 severity assessment criteria for acute cholangitis**

Given these inconveniences of TG07 in clinical practice, revision was made to improve severity assessment strategies upon diagnosis to allow provision of immediate source control of infection among patients with acute cholangitis. To begin with, we examined the items reported as predictive factors of poor prognosis among patients with acute cholangitis and those who required urgent biliary drainage. Furthermore, factors endoscopic gastroenterologists value in determining the timing of biliary drainage were integrated, except for the factors that define Grade III cases (severe cases). Factors which were inappropriate for use as items of severity assessment were excluded. Consequently, five factors—hypalbuminemia, elderly patients, high fever, leukocytosis and hyperbilirubinemia—were extracted [8, 32]. Cases with two of these five factors present were classified as Grade II (moderate) [8].

<table>
<thead>
<tr>
<th>Disease</th>
<th>N</th>
<th>Charcot’s triad (%)</th>
<th>Fever (%)</th>
<th>Jaundice (%)</th>
<th>Abdominal pain (%)</th>
<th>Reynolds’ pentad (%)</th>
<th>Shock (%)</th>
<th>Disturbed consciousness (%)</th>
<th>History of biliary diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welch [2]</td>
<td>ASC</td>
<td>5</td>
<td>50</td>
<td>80</td>
<td>60</td>
<td>0</td>
<td>20</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AOSC</td>
<td>15</td>
<td>50</td>
<td>88</td>
<td>67</td>
<td>33</td>
<td>27</td>
<td>46.7</td>
<td></td>
</tr>
<tr>
<td>Boey [3]</td>
<td>AC</td>
<td>99</td>
<td>69.7</td>
<td>93.9</td>
<td>78.8</td>
<td>87.9</td>
<td>5.1</td>
<td>16.2</td>
<td>16.2</td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td>14</td>
<td>7</td>
<td>57</td>
<td>28</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NonSC</td>
<td>72</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Csendes [9]</td>
<td>ASC</td>
<td>512</td>
<td>22</td>
<td>38.7</td>
<td>65.4</td>
<td>92.2</td>
<td>7</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Thompson [10]</td>
<td>AC</td>
<td>66</td>
<td>About 60</td>
<td>100</td>
<td>66</td>
<td>59</td>
<td>7</td>
<td>9</td>
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<tr>
<td></td>
<td>Gigot [11]</td>
<td>AC</td>
<td>412</td>
<td>72</td>
<td>100</td>
<td>61.5</td>
<td>100</td>
<td>7.7</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>O’Connor [12]</td>
<td>SC</td>
<td>19</td>
<td>53</td>
<td>5</td>
<td>47</td>
<td>11</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>NonSC</td>
<td>46</td>
<td>63</td>
<td>9</td>
<td>26</td>
<td>15</td>
<td>9</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Lai [13]</td>
<td>Severe AC</td>
<td>86</td>
<td>56</td>
<td>66</td>
<td>93</td>
<td>90</td>
<td>64</td>
<td>27.9</td>
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<tr>
<td>Haupert [14]</td>
<td>ASC</td>
<td>13</td>
<td>15.4</td>
<td>100</td>
<td>61.5</td>
<td>100</td>
<td>7.7</td>
<td>23.1</td>
<td>7.7</td>
</tr>
</tbody>
</table>

AC acute cholangitis, SC suppurative cholangitis, AOSC acute obstructive suppurative cholangitis

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Table 3 Incidence of clinical manifestations of acute cholangitis

Table 4  TG13 severity assessment criteria for acute cholangitis

**Grade III (Severe) acute cholangitis**

“Grade III” acute cholangitis is defined as acute cholangitis that is associated with the onset of dysfunction in at least one of any of the following organs/systems:

1. Cardiovascular dysfunction  
   Hypotension requiring dopamine ≥5 µg/kg per min, or any dose of norepinephrine
2. Neurological dysfunction  
   Disturbance of consciousness
3. Respiratory dysfunction  
   PaO$_2$/FiO$_2$ ratio <300
4. Renal dysfunction  
   Oliguria, serum creatinine >2.0 mg/dl
5. Hepatic dysfunction  
   PT-INR >1.5
6. Hematological dysfunction  
   Platelet count <100,000/mm$^3$

**Grade II (moderate) acute cholangitis**

“Grade II” acute cholangitis is associated with any two of the following conditions:

1. Abnormal WBC count (>12,000/mm³, <4,000/mm³)
2. High fever (≥39 °C)
3. Age (≥75 years old)
4. Hyperbilirubinemia (total bilirubin ≥5 mg/dL)
5. Hypoalbuminemia (<STD x 0.7)

**Grade I (mild) acute cholangitis**

“Grade I” acute cholangitis does not meet the criteria of “Grade III (severe)” or “Grade II (moderate)” acute cholangitis at initial diagnosis.

Notes

Early diagnosis, early biliary drainage and/or treatment for etiology, and antimicrobial administration are fundamental treatments for acute cholangitis classified not only as Grade III (severe) and Grade II (moderate) but also Grade I (mild).

Therefore, it is recommended that patients with acute cholangitis who do not respond to the initial medical treatment (general supportive care and antimicrobial therapy) undergo early biliary drainage or treatment for etiology (see flowchart).

Cited from Ref. [8]

STD lower limit of normal value

**TG13 severity assessment criteria for acute cholangitis**

The revised assessment criteria for acute cholangitis are shown in Table 4.

The severity of acute cholangitis is classified as follows:

- **Grade III (severe):** presence of organ dysfunction.
- **Grade II (moderate):** risk of increased severity without early biliary drainage.
- **Grade I (mild):**

The severity assessment criteria are very important for determining the treatment strategy for acute cholangitis, especially for Grade II cases which may progress to Grade III without immediate intervention. Treatment of acute cholangitis requires “treatment for causes” for cases with any severity, along with the administration of antimicrobial agents and biliary drainage.

**Q7. What morbid conditions are referred to as ‘Grade III (severe)’ in assessing severity for acute cholangitis?**

‘Severe’ is referred to as a condition that gives rise to organ dysfunction due to acute cholangitis requiring intensive care such as respiratory and circulatory support.

**Q8. What morbid conditions are referred to as ‘moderate’ in assessing severity for acute cholangitis?**

‘Grade II (moderate)’ is referred to as a condition suggesting cholangitis requiring emergent or early biliary drainage without presence of organ dysfunction, but with risks of progression to Grade III.

**Q9. How are TG13 Severity Assessment Criteria for acute cholangitis appraised?**

TG13 Severity Assessment Criteria for Acute Cholangitis is more suitable and practical for clinical use than TG07, because of enabling us to identify Grade II which requires early biliary drainage at the time of initial diagnosis (recommendation 1, level B).
According to TG13 severity assessment criteria, the number of cases for which biliary drainage was carried out within 48 h included 50 Grade III cases (69.4 %), 129 Grade II cases (59.7 %), and 181 Grade I cases (54.0 %). However, many of the Grade I cases that had undergone biliary drainage within 48 h were accounted for as the treatment of etiology such as bile stones. Grade I cases that had undergone biliary drainage as an urgent treatment were very few in number [8].

Q10. Are the acute cholangitis cases that meet Charcot’s triad considered as severe cases?

The presence or absence of Charcot’s triad does not reflect severity. So, cases that meet Charcot’s triad are not necessarily assessed as severe (level B).

In the multi-center analysis, of the 110 cases of acute cholangitis that showed Charcot’s triad, only 13 cases (11.8 %) were classified as Grade III. Compared with the cases that did not show Charcot’s triad, there were no differences in terms of severity. Furthermore, many (approximately 80 %) of the Grade III cases in TG13 failed to satisfy Charcot’s triad [8]. The presence or absence of conformity with Charcot’s triad was not associated with severity. Cases that meet Charcot’s criteria are not necessarily classified as severe cases.

Conflict of interest  None.

References

TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos)

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Abstract Since its publication in 2007, the Tokyo Guidelines for the management of acute cholangitis and cholecystitis (TG07) have been widely adopted. The validation of TG07 conducted in terms of clinical practice has shown that the diagnostic criteria for acute cholecystitis are highly reliable but that the definition of definite diagnosis is ambiguous. Discussion by the Tokyo Guidelines Revision Committee concluded that acute cholecystitis should be suspected when Murphy’s sign, local inflammatory findings in the gallbladder such as right upper quadrant abdominal pain and tenderness, and fever and systemic inflammatory reaction findings detected by blood tests are present but that definite diagnosis of acute cholecystitis can be made only on the basis of the imaging of ultrasonography, computed tomography or scintigraphy (HIDA scan). These proposed diagnostic criteria provided better specificity and accuracy rates than the TG07 diagnostic criteria. As for the severity assessment criteria in TG07, there is evidence that TG07 resulted in clarification of the concept of severe acute cholecystitis. Furthermore, there is evidence that severity assessment in TG07 has led to a reduction in the mean duration of hospital stay. As for the factors used to establish a moderate grade of acute cholecystitis, such as leukocytosis, ALP, old age, diabetes, being...
male, and delay in admission, no new strong evidence has been detected indicating that a change in the criteria used in TG07 is needed. Therefore, it was judged that the severity assessment criteria of TG07 could be applied in the updated Tokyo Guidelines (TG13) with minor changes. TG13 presents new standards for the diagnosis, severity grading and management of acute cholecystitis.


Keywords  Acute cholecystitis · Diagnostic criteria · Severity grading · Diagnostic imaging · Guidelines

Introduction

Acute cholecystitis is a disease frequently encountered in daily practice presenting with right hypochondrial pain as the main symptom [1–4]. However, there were no diagnostic criteria and severity assessment criteria for this commonplace disease before the publication in 2007 of the Tokyo Guidelines for the management of acute cholangitis and cholecystitis (TG07) in the Journal of Hepato-Biliary-Pancreatic Surgery (vol. 14.1:1–121, 2007). There is a treatise in TG07 released with the expectation that it will present international guidelines for improvement in the diagnosis and treatment of acute cholecystitis [5].

The diagnostic criteria in TG07 were set at high sensitivity to provide medical care suitable for a larger number of cases and the sensitivity has been reported as 84.9 % on the basis of the test results for TG07 diagnostic criteria [6]. TG07 guidelines have already been recognized as the diagnostic criteria to be recommended in today’s medical care for acute cholecystitis [1]; however, guidelines should achieve further evolution. In view of the current situation where diagnostic imaging such as ultrasonography (US), CT and scintigraphy (HIDA scan) are frequently used for the definite diagnosis of acute cholecystitis, integration of such diagnostic modalities in guidelines is the main theme in the present revision.

Acute cholecystitis sometimes requires emergency treatment for morbidities such as gangrenous cholecystitis, emphysematous cholecystitis and gallbladder torsion. An indication that it may require high-level skills is given by its other name, “difficult gallbladder” [7, 8]. In making a diagnosis of acalculous cholecystitis, challenges may be encountered. There may be cases with a poor prognosis [9, 10]. The severity assessment criteria in TG07 defined severe acute cholecystitis as acute cholecystitis accompanying organ dysfunction directly related to vital prognosis. Actually, the overall mortality rate of acute cholecystitis is approximately 0.6 % [11, 12], and that of severe cases was reported in TG07 as 6.0 % [13]. Acute cholecystitis is essentially not a disease with a high mortality rate. However, it was thought that guidelines should make it clear that appropriate management with appropriate use of severity assessment criteria does lead to improved vital prognosis.

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Six years have passed since the publication of TG07 and the Tokyo Guidelines Revision Committee has been charged with examining the results of the validation that has been conducted so far, involving problems such as inconvenience of their use in actual clinical settings [6, 13–15]. Considering the progress of diagnostic technology and detection of new evidence, diagnostic criteria and severity grading revised as the updated Tokyo Guidelines (TG13) are presented in accordance with actual clinical settings [16].

Diagnostic criteria for acute cholecystitis; TG13

**Background**

**Murphy’s sign**

**Q1. How large is the diagnostic capacity of Murphy’s sign for acute cholecystitis?**

*Murphy’s sign shows high specificity, however the sensitivity has been reported low. It is not applicable in making a diagnosis of acute cholecystitis due to the low sensitivity (level D).*

Murphy’s sign refers to where the patient stops breathing due to pain when an examiner touches the inflammatory gallbladder of the patient. In 1903, Murphy [17] described the condition as a sign of cholelithiasis. Murphy’s sign has also been widely known as a diagnostic factor of acute cholecystitis. Substantial numbers of clinicians throughout the world providing treatment for acute cholecystitis refer to Murphy’s sign. It has been reported in previous studies to have a sensitivity of 50–65 % and a high specificity of 79 % [18] or 96 % [2] for the diagnosis of acute cholecystitis although the sensitivity was once reported to be as low as 20.5 %, while the specificity was 87.5 % [6]. It has a weak point in that an accurate diagnosis of cholecystitis can be made when Murphy’s sign is present, while its absence does not necessarily mean the absence of cholecystitis.

**TG07 diagnostic criteria for acute cholecystitis**

**Q2. How are the diagnostic criteria for acute cholecystitis in TG07 appraised?**

*Although the sensitivity had been improved compared with Murphy’s sign, TG07 diagnostic criteria have limitations and their validity is insufficient for using them to make a definite diagnosis (level D).*

At an international consensus meeting held in Tokyo in 2007, the world’s first diagnostic criteria were presented in the Tokyo Guidelines for the management of acute cholangitis and cholecystitis; these are international clinical practice guidelines. According to a review referring to these diagnostic criteria, a definite diagnosis of acute cholecystitis can be made when a local sign or symptom and a systemic sign are present, and test imaging provides confirmation [1]. There is a report of cases for which favorable sensitivity (84.9 %) and specificity (50.0 %) have been achieved when using TG07 diagnostic criteria in clinical practice [6]. Multicenter analysis by the Tokyo Guidelines Revision Committee showed that the sensitivity was 92.1 % and the specificity was 93.3 % in TG07 [16].

**Revision of TG07 diagnostic criteria for acute cholecystitis**

The most important problem in TG07 was that the criteria for definite diagnosis were ambiguous and difficult to use. In TG07, there were two categories determining the definite diagnosis of acute cholecystitis. “Definite diagnosis 1”: To obtain a definite diagnosis one item in A and one item in B had to be positive. “Definite diagnosis 2”: Imaging findings (criterion C) confirmed the diagnosis when acute cholecystitis was suspected clinically.

The Tokyo Guidelines Revision Committee concluded that the term “definite diagnosis” could not be supported in current practice without positive diagnostic imaging studies. We have now changed the expressions: “suspected” diagnosis is achieved when one item from section A and one item in B had to be positive. “Definite” diagnosis is achieved when imaging findings characteristic of acute cholecystitis (item C) are also present (one item in A + one item in B + C) [16].

**TG13 diagnostic criteria for acute cholecystitis**

The revised diagnostic criteria for acute cholecystitis are shown in Table 1.

A diagnosis of acute cholecystitis is made as follows according to diagnostic criteria. When acute cholecystitis is suspected from clinical signs and results of blood tests, a definite diagnosis is made after it has been confirmed by diagnostic imaging.

**Q3. How are the diagnostic criteria for acute cholecystitis in TG13 appraised?**

*TG13 diagnostic criteria of acute cholecystitis have a high sensitivity and a high specificity (recommendation 1, level B).*
An assessment by multicenter analysis of TG13 diagnostic criteria shows that sensitivity (91.2 %) and specificity (96.9 %) are favorable and that diagnostic capacity is almost the same as that in TG07 [16]. It is pointed out that the diagnostic criteria for acute cholecystitis in TG07 have limitations in that patients with few systemic symptoms tend to be underdiagnosed [1]. There is also a report showing that neither fever nor an elevated white cell count were observed in 16 % of cases with gangrenous cholecystitis or in 28 % of cases with non-gangrenous cholecystitis [8]. It is important that the diagnosis is confirmed repeatedly for cases with suspected cholecystitis.

Clinical context and manifestations

Q4. What is the most important physical manifestation for making a diagnosis of acute cholecystitis?

The most typical clinical sign of acute cholecystitis is abdominal pain.

Laboratory data

What is the most important blood test for making a diagnosis of acute cholecystitis?

There are no specific blood tests for making a diagnosis of acute cholecystitis. So, the diagnosis can be made if the following findings are present: general inflammatory findings (abnormal white blood cell count, elevated CRP level), an increase in blood cell count of more than 10000 mm$^3$/dl, an increase in CRP level of more than 3 mg/dl, and a mild increase of serum enzymes in the hepato-biliary-pancreatic system and bilirubin.

The bilirubin level may rise to 4 mg/dl (68 μmol/dl) in the absence of complications [1]. When ultrasonography shows findings that suggest acute cholecystitis and a CRP level exceeding 3 mg/dl, a diagnosis of acute cholecystitis can be made with 97 % sensitivity, 76 % specificity, and 95 % positive predictive value [24].

Table 1: TG13 diagnostic criteria for acute cholecystitis

<table>
<thead>
<tr>
<th>A. Local signs of inflammation etc.</th>
<th>B. Systemic signs of inflammation etc.</th>
<th>C. Imaging findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Murphy’s sign</td>
<td>(1) Fever, (2) elevated CRP, (3) elevated WBC count</td>
<td></td>
</tr>
<tr>
<td>(2) RUQ mass/pain/tenderness</td>
<td></td>
<td>Imaging findings characteristic of acute cholecystitis</td>
</tr>
<tr>
<td>RUQ right upper abdominal quadrant, CRP C-reactive protein, WBC white blood cell</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Incidence of clinical symptoms of acute cholecystitis

<table>
<thead>
<tr>
<th>Study</th>
<th>RUQ pain (%)</th>
<th>Epigastralgia (%)</th>
<th>Nausea (%)</th>
<th>Emesis (%)</th>
<th>Fever (%)</th>
<th>Rebound (%)</th>
<th>Guarding (%)</th>
<th>Rigidity (%)</th>
<th>Mass (%)</th>
<th>Murphy’s sign (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brewer [19]</td>
<td>26</td>
<td>77</td>
<td>30 (≥38 °C)</td>
<td>35</td>
<td>58</td>
<td>3.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schofield [20]</td>
<td>64</td>
<td>83</td>
<td>31 (&gt;37.5 °C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staniland [21]</td>
<td>100</td>
<td>38</td>
<td>34</td>
<td>About 80</td>
<td>About 70</td>
<td>About 30</td>
<td>About 45</td>
<td>About 10</td>
<td>About 25</td>
<td></td>
</tr>
<tr>
<td>Halas [3]</td>
<td>191</td>
<td>93</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singer [22]</td>
<td>40</td>
<td></td>
<td></td>
<td>10 (&gt;38.0 °C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>Adedeji [23]</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48</td>
</tr>
</tbody>
</table>

RUQ right upper abdominal quadrant
Imaging findings

Ultrasonography (US)

Q5. Which type of diagnostic imaging method should be used, first of all, for making a diagnosis of acute cholecystitis?

Ultrasonography should be performed at the initial consultation for all cases for which acute cholecystitis is suspected (recommendation 1, level A).

Ultrasonography is the test that should be performed first of all for every case of suspected acute cholecystitis. Even emergency physicians who are not specialists in ultrasonography are able to make a satisfactory diagnosis [25, 26].

In view of its convenience and lack of invasiveness, ultrasonography should be considered the first option among morphological tests for this morbidity.

Q6. How large is the diagnostic capacity of ultrasonography for acute cholecystitis?

Ultrasonography shows 50–88% sensitivity and 80–88% specificity.

A report by Chatziioannou et al. [27] discussing 107 cases of acute cholecystitis in terms of the diagnostic capacity of ultrasonography has found that sensitivity is 50%, specificity 88%, PPV 64%, NPV 80%, and accuracy 77%.

On the basis of a meta-analysis of five treatises involving a total of 532 cases, Shea et al. show that the diagnostic capability of ultrasonography for acute cholecystitis: sensitivity 88% (95% CI 0.74–1.00) and specificity 80% (95% CI 0.62–0.98) [28]. The diagnostic capacity of ultrasonography for acute cholecystitis is generally thought to be good.

Q7. What are the ultrasonographic imaging findings characteristic of acute cholecystitis?

They are mainly enlarged gallbladder, thickening of the gallbladder wall, gallbladder stones, and debris echo.

A diagnosis of acute calculous cholecystitis can be made radiologically when the following findings are present at the same time: thickening of the gallbladder wall (5 mm or greater), pericholecystic fluid, or direct tenderness when the probe is pushed against the gallbladder (ultrasoundographic Murphy’s sign) [1]. Other ultrasonographic findings may include gallbladder enlargement, gallbladder stones, debris echo and gas imaging (Fig. 1).

However, due to differences among reports in the frequency of the occurrence of individual findings, sensitivity, and specificity, diagnosis should be made after a comprehensive judgment has been made of individual findings [29, 30] (Supplement Table 1).

There are many diagnostic modalities enabling depiction of stones. However, there is a report showing that bile stones could be depicted by ultrasonography in only 13% of cases (1 of 7 cases). Therefore, the use of other

Table 3  Diagnostic capability of clinical symptoms for acute cholecystitis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Summary LR (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>2</td>
<td>1135</td>
<td>1.1–1.7</td>
<td>0.5–0.9</td>
<td>0.65 (0.57–0.73)</td>
</tr>
<tr>
<td>Emesis</td>
<td>4</td>
<td>1338</td>
<td>1.5 (1.1–2.1)</td>
<td>0.6 (0.3–0.9)</td>
<td>0.71 (0.65–0.76)</td>
</tr>
<tr>
<td>Fever</td>
<td>8</td>
<td>1292</td>
<td>1.5 (1.0–2.3)</td>
<td>0.9 (0.8–1.0)</td>
<td>0.35 (0.31–0.38)</td>
</tr>
<tr>
<td>Guarding</td>
<td>2</td>
<td>1170</td>
<td>1.1–2.8</td>
<td>0.5–1.0</td>
<td>0.45 (0.37–0.54)</td>
</tr>
<tr>
<td>Murphy’s sign</td>
<td>3</td>
<td>565</td>
<td>2.8 (0.8–8.6)</td>
<td>0.5 (0.2–1.0)</td>
<td>0.65 (0.58–0.71)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>669</td>
<td>1.0–1.2</td>
<td>0.6–1.0</td>
<td>0.77 (0.69–0.83)</td>
</tr>
<tr>
<td>Rebound</td>
<td>4</td>
<td>1381</td>
<td>1.0 (0.6–1.7)</td>
<td>1.0 (0.8–1.4)</td>
<td>0.30 (0.23–0.37)</td>
</tr>
<tr>
<td>Rectal tenderness</td>
<td>2</td>
<td>1170</td>
<td>0.3–0.7</td>
<td>1.0–1.3</td>
<td>0.08 (0.04–0.14)</td>
</tr>
<tr>
<td>Rigidity</td>
<td>2</td>
<td>1140</td>
<td>0.50–2.32</td>
<td>1.0–1.2</td>
<td>0.11 (0.06–0.18)</td>
</tr>
<tr>
<td>RUQ mass</td>
<td>4</td>
<td>408</td>
<td>0.8 (0.5–1.2)</td>
<td>1.0 (0.9–1.1)</td>
<td>0.21 (0.18–0.23)</td>
</tr>
<tr>
<td>RUQ pain</td>
<td>5</td>
<td>949</td>
<td>1.5 (0.9–2.5)</td>
<td>0.7 (0.3–1.6)</td>
<td>0.81 (0.78–0.85)</td>
</tr>
<tr>
<td>RUQ tenderness</td>
<td>4</td>
<td>1001</td>
<td>1.6 (1.0–2.5)</td>
<td>0.4 (0.2–1.1)</td>
<td>0.77 (0.73–0.81)</td>
</tr>
</tbody>
</table>

Cited from Ref. [18]

RUQ right upper abdominal quadrant, LR likelihood ratio, CI confidence interval
techniques, such as MR cholangiography (MRCP), should be considered depending on conditions [31].

According to a report by Cohan et al. [32] who examined 51 cases that had developed thickening of the gallbladder wall, including 13 cases of acute cholecystitis, a so-called sonolucent layer (hypoechoic layer), referred to as a low-echo zone, within the gallbladder wall showed 8% sensitivity (95% CI 0–22.1) and 71.0% specificity (95% CI 56.6–85.5). Therefore, it cannot be considered a good diagnostic measure for acute cholecystitis. The presence of a low-echoic area with an irregular multiple structure showing 62% sensitivity (95% CI 35.1–88.0) and 100% specificity (95% CI 100–100) has a higher diagnostic value [32] (Supplement Fig. 1; Supplement Movie 1).

**Q8. What findings are to be noted when ultrasonography is conducted for cases for which acute cholecystitis is suspected?**

Ultrasoundographic Murphy’s sign shows high specificity and it is useful for making a diagnosis.

Ultrasoundographic Murphy’s sign refers to the pain that occurs when the gallbladder is pressed while it is being depicted with an ultrasonographic probe. It is superior to the ordinary Murphy’s sign in that it is possible to press the gallbladder accurately. On the basis of the examination of 219 cases of right upper quadrant abdominal pain, Ralls et al. have reported that ultrasonographic Murphy’s sign is somewhat inferior to the ordinary Murphy’s sign in sensitivity (63.0%, 95% CI 49.1–77.0%), although it is superior in specificity (93.6%, 95% CI 90.0–97.3%) [33]. According to Bree et al. who examined 200 cases (of which 73 cases were acute cholecystitis) with complaints of right upper quadrant abdominal pain, the sensitivity of ultrasonographic Murphy’s sign is good (86.3%; 95% CI 78.4–94.2%) although the specificity is inferior (35.0%; 95% CI 26.4–43.0%), so the presence of bile stones should be taken into account when a diagnosis is made [34]. Ultrasonographic Murphy’s sign can also be used to distinguish acute cholecystitis from cases of Murphy’s sign.

**Fig. 1** US images of acute cholecystitis. Gallbladder swelling, wall thickening with hypoechoic layer, massive debris, and stone impaction are demonstrated.

**Fig. 2** US images of perforated duodenal ulcer case with positive Murphy’s sign (non-ultrasonographic), increased white blood cell count and elevated C-reactive protein. Wall thickening of the anterior wall of the duodenal bulb as well as a large wall defect accompanied with extramural air is clearly demonstrated by US.
positive due to other diseases and for diagnosis of the causative disease, such as duodenal ulcer (Fig. 2).

Q9. Is color or power Doppler imaging useful for making a diagnosis of acute cholecystitis?

The findings of power Doppler imaging are useful for making a diagnosis of acute cholecystitis (recommendation 2, level C).

Soyer et al. examined 129 cases complaining of acute pain in the upper right quadrant abdomen and reported that the diagnostic capacity for acute cholecystitis on the basis of Doppler sonographic findings were: sensitivity 95 %, specificity 100 %, accuracy 99 %, PPV 100 %, and NPV 99 %, exceeding that of the B-mode Doppler sonography (sensitivity 86 %, specificity 99 %, accuracy 92 %, PPV 92 %, and NPV 87 %) [35] (Supplement Table 2).

On the other hand, Tessler et al. [36] who examined a small number of cases have found that intramural Doppler signals are also observed in normal cases and that signal depiction becomes more remarkable after food intake. Furthermore, Jeffrey et al. carried out detailed discussion of 54 cases undergoing surgery for cholecystitis and 115 normal controls including the area of depiction and have found that the presence or absence of signal depiction alone is not a finding specific to cholecystitis. They looked at the presence of a blood flow signal extending over more than half of the anterior wall (26 % occurrence rate compared with 2 % for normal cases), and discovered that the signal depicted on the bottom is a more specific finding (the frequency of occurrence being 0 % for normal cases and 19 % for cholecystitis cases) [37].

On the basis of the above observations, it may be possible to make a diagnosis of cholecystitis by means of color or power Doppler sonography. However, the detective capacity of Doppler signals is influenced by the performance and settings of the instruments used and, and the physique of subjects. Careful judgment should be made when using Doppler sonographic findings as the only reference findings including B-mode findings (Supplement Fig. 2).

CT findings of acute cholecystitis were reported as: GB distention (41 %), gallbladder wall thickening (59 %), pericholecystic fat density (52 %), pericholecystic fluid collection (31 %), subserosal edema (31 %), and high-attenuation gallbladder bile (24 %) (Fig. 3; Supplement Fig. 3) [38].

Anatomically, a part of the cholecystic vein directly drains into the liver parenchyma surrounding the gallbladder fossa. In patients with acute cholecystitis, venous blood flow from the gallbladder wall into the liver increases. So, the arterial phase of dynamic CT shows transient focal enhancement of the liver adjacent to the inflamed gallbladder (Fig. 3; Supplement Fig. 3) [39–42]. This enhancement disappears during the portal and equilibrium phase.

In mild acute cholecystitis, gallbladder distention without wall thickening or edema are the only signs on CT. Because gallbladder size is variable depending on the individual, gallbladder distention is difficult to evaluate on diagnostic imaging (such as ultrasonography or non-contrast CT) of acute cholecystitis. Dynamic CT, especially during the arterial phase, is very useful in mild cholecystitis because of the high sensitivity of transient focal enhancement of the liver adjacent to the gallbladder [41].

Tc-HIDA scans

Hepatobiliary scintigraphy involves intravenous injection of technetium-labeled analogues of iminodiacetic acid, which are excreted into the bile. The failure of the gallbladder to fill within 60 min after administration of the tracer indicates that the cystic duct is obstructed and has a sensitivity of 80–90 % for acute cholecystitis. The false positive rate of 10–20 % is largely explained by cystic duct obstruction induced by chronic inflammation, although in some cases normal gallbladders do not fill due to insufficient resistance at the sphincter of Oddi. When the cystic duct is patent (i.e., no cholecystitis), the gallbladder is normally visualized within 30 min. The “rim sign” is a blush of increased pericholecystic radioactivity, which is present in about 30 % of patients with acute cholecystitis and in about 60 % with acute gangrenous cholecystitis [1]. In patients with suspected acute cholecystitis, hepatobiliary scintigraphy has significantly higher specificity [27] and higher accuracy [43] than ultrasonography. Nevertheless, ultrasonography is usually preferred as the first test because of its immediate availability, easy access, a lack of interference by elevated serum bilirubin levels (since cholestasis interferes with biliary excretion of the agents used for scintigraphy), the absence of ionizing radiation, and the...
ability to provide information regarding the presence of stones [1].

Severity assessment criteria for acute cholecystitis; TG13

Background

Patients with acute cholecystitis may present a spectrum of disease stages ranging from a mild, self-limited illness to a fulminant and potentially life-threatening disease. In fact, the overall mortality rate of acute cholecystitis is approximately 0.6 % [11, 12]. There were no severity assessment criteria for this common disease until 2007 [16].

TG07 severity assessment criteria for acute cholecystitis

The severity assessment criteria were first presented throughout the world in TG07 [5], where the severity grading of acute cholecystitis was classified into the following 3 categories: “mild (Grade I)”, “moderate (Grade II)” and “severe (Grade III)”. Severe (Grade III) acute cholecystitis was defined as acute cholecystitis associated with organ dysfunction.

Moderate (Grade II) acute cholecystitis was defined as acute cholecystitis in which the degree of acute inflammation is likely to be associated with increased operative difficulty in performing cholecystectomy [44–49].

Mild (Grade I) acute cholecystitis was defined as occurring in a patient who has no findings of organ dysfunction and mild disease in the gallbladder, enabling cholecystectomy as a safe and low risk procedure. These patients do not have a severity index that meets the criteria for “moderate (Grade II)” and “severe (Grade III)” acute cholecystitis in TG07.

There are reports that discussed and appraised the TG07 severity assessment criteria. According to those papers, the distribution varies as follows: 39.3–68.5 % of the cases were classified as Grade I, 25.5–59.5 % as Grade II, and 1.2–6 % as Grade III [14, 15]. In addition, there is a report

Fig. 3 Acute cholecystolithiasis (62-year-old male). Non-contrast CT (a) shows gallbladder distention, wall thickening, and gallstone (arrow). The arterial phase of contrast-enhanced dynamic CT (b, c, f) shows gallbladder wall edema (asterisk) and focal hepatic enhancement adjacent to the gallbladder (arrowheads). Hepatic enhancement disappears on the equilibrium phase of CT (d, e)
suggesting that the assessment criteria have contributed to a decrease in the period of hospital stay [13]. This demonstrates that TG07 severity assessment criteria have received good appraisal; there has so far been no treatise or report that has pointed out matters to be improved and weak points of TG07.

Revision of severity grading for acute cholecystitis; TG07

There are reports on poor prognostic factors of acute cholecystitis and those enabling the estimation of emergency surgery. Factors reported after 2000 include leukocytosis [13, 15, 50–55], ALP [50, 56, 57], old age [53, 54, 58], diabetes [51, 52], male sex [51, 53], and admission delay [55]. There are also reports of imaging findings such as ultrasonographic findings of gallbladder wall thickening [53] and common bile duct distention [57]. To date there has been a small number of new reports of AST, ALT, LDH, BUN, and creatinine. The severity assessment criteria were reconsidered by the Tokyo Guidelines Revision Committee with new information, evidence, and evaluations of TG07. Consequently, the TG07 severity assessment criteria did not have significant problems that required major revision of the definitions or structures [16]. However, minor changes were made to the description of Grade III severity: dopamine and norepinephrine were both considered as evidence of cardiovascular dysfunction consistent with the SOFA scoring system [59].

TG13 severity assessment criteria for acute cholecystitis

The revised severity grading for acute cholecystitis is shown in Table 4. TG07 severity assessment criteria have been adopted in TG13 with minor changes [16].

Q11. What morbid conditions are referred to as severe in assessing severity for acute cholecystitis?

“Severe” is referred to as a condition that has developed organ dysfunction as circulatory failure, consciousness disturbance, respiratory failure, renal failure, hepatic failure or blood coagulation disorder. Intensive care with respiratory and circulatory management should be performed.

Acute cholecystitis has a better outcome/prognosis than acute cholangitis but requires prompt treatment when gangrenous cholecystitis, emphysematous cholecystitis, or torsion of the gallbladder are present. The progression of acute cholecystitis from the mild/moderate to the severe form means the development of multiple organ dysfunction syndrome (MODS). Organ dysfunction scores, such as Marshall’s multiple organ dysfunction (MOD) score and the sequential organ failure assessment (SOFA) score [60], are sometimes used to evaluate organ dysfunction in critically ill patients. The six factors involved in organ dysfunction have therefore been adopted in TG07 as factors that enable severity assessment.

Table 4 TG13 severity grading for acute cholecystitis

<table>
<thead>
<tr>
<th>Grade III (severe) acute cholecystitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated with dysfunction of any one of the following organs/systems:</td>
</tr>
<tr>
<td>1. Cardiovascular dysfunction</td>
</tr>
<tr>
<td>2. Neurological dysfunction</td>
</tr>
<tr>
<td>3. Respiratory dysfunction</td>
</tr>
<tr>
<td>4. Renal dysfunction</td>
</tr>
<tr>
<td>5. Hepatic dysfunction</td>
</tr>
<tr>
<td>6. Hematological dysfunction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade II (moderate) acute cholecystitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated with any one of the following conditions:</td>
</tr>
<tr>
<td>1. Elevated white blood cell count (&gt;18,000/mm³)</td>
</tr>
<tr>
<td>2. Palpable tender mass in the right upper abdominal quadrant</td>
</tr>
<tr>
<td>3. Duration of complaints &gt;72 h</td>
</tr>
<tr>
<td>4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade I (mild) acute cholecystitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does not meet the criteria of “Grade III” or “Grade II” acute cholecystitis. Grade I can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure</td>
</tr>
</tbody>
</table>
Q12. What morbid conditions are referred to as moderate in assessing severity for acute cholecystitis?

"Moderate" is referred to as a condition of acute cholecystitis without organ dysfunction but with its risk, accompanying serious local complication, and for which cholecystectomy and biliary drainage are to be carried out immediately.

Q13. In making a diagnosis of acute cholecystitis, what are the factors that enable the assessment of moderate cases?

The presence of leucocytosis, palpable right upper quadrant abdominal pain, persistence of symptoms for more than 72 hours after onset or severe inflammation findings.

TG07 included findings such as an elevated level of WBC and imaging findings in assessment items specifically applied in moderate (Grade II) acute cholecystitis. Included in these items is evidence such as leukocytosis (>18,000 mm$^3$) detected at the time of hospitalization, prognostic factors that contribute to the change of surgical techniques from laparoscopic surgery to open surgery, and the time of symptom persistence (of more than 72 h) from the onset of symptoms [44, 61]. The criteria for Grade II (moderate) acute cholecystitis can be defined as acute cholecystitis associated with local inflammatory conditions that make cholecystectomy difficult.

As for the factor “old age”, the following statement had been adopted to call attention in TG07; however the statement is useful for the revised edition, too. “Elderly” per se is not a criterion for severity itself but indicates a propensity to progress to the severe form, and thus is not included in the criteria for severity assessment [5].

When acute cholecystitis is accompanied by acute cholangitis, the criteria for the severity assessment of acute cholangitis should also be taken into account [62, 63].

Q14. What are the findings to be noted when the assessment of gangrenous cholecystitis and emphysematous cholecystitis is carried out by means of ultrasonography?

Irregular thickening of the gallbladder wall and imaging of the ruptured gallbladder wall should be noted.

Through the discussion of 19 cases of gangrenous cholecystitis, Jeffrey et al. [7] found that the membranous structure of the lumen within the gallbladder is observed in 31.6% (6 cases), irregular thickening of the gallbladder wall in 47.4% (9 cases), both of these findings in 21.1% (4 cases), and either of these findings in 57.9% (11 cases). Regarding perforation, Forsberg et al. [64] also reported on the basis of the discussion involving 24 cases of perforation and 21 cases of acute cholecystitis without perforation that no specific findings were observed, although a slightly thickened wall was observed (3–20 mm, mean 7 mm, for cases with perforation; 2–13 mm, mean 5.3 mm, for cases without perforation). On the other hand, according to Sood et al. [65] depiction of the ruptured wall as a direct finding of gallbladder perforation was able to be made with ultrasonography in 70% (16 of 23 cases) and with CT in 78% (14 of 18 cases). Depending on the performance of the instrument used, it can be assumed that the diagnosis can be made for considerable numbers of cases (Fig. 4; Supplement Movie 2).

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provided us with great support and guidance in the preparation of the Guidelines.

Conflict of interest None.

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increases attenuation in the liver at biphasic, contrast enhanced dynamic CT. Radiology. 1997;204:723–8.
TG13 flowchart for the management of acute cholangitis and cholecystitis

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Abstract  We propose a management strategy for acute cholangitis and cholecystitis according to the severity assessment. For Grade I (mild) acute cholangitis, initial medical treatment including the use of antimicrobial agents may be sufficient for most cases. For non-responders to initial medical treatment, biliary drainage should be considered. For Grade II (moderate) acute cholangitis, early biliary drainage should be performed along with the administration of antibiotics. For Grade III (severe) acute cholangitis, appropriate organ support is required. After hemodynamic stabilization has been achieved, urgent endoscopic or percutaneous transhepatic biliary drainage should be performed. In patients with Grade II (moderate) and Grade III (severe) acute cholangitis, treatment for the underlying etiology including endoscopic, percutaneous, or surgical treatment should be performed after the patient’s general condition has been improved. In patients with Grade I (mild) acute cholangitis, treatment for etiology such as endoscopic sphincterotomy for choledocholithiasis might be performed simultaneously, if possible, with biliary drainage. Early laparoscopic cholecystectomy is the first-line treatment in patients with Grade I (mild) acute cholecystitis.

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cholecystitis while in patients with Grade II (moderate) acute cholecystitis, delayed/elective laparoscopic cholecystectomy after initial medical treatment with antimicrobial agent is the first-line treatment. In non-responders to initial medical treatment, gallbladder drainage should be considered. In patients with Grade III (severe) acute cholecystitis, appropriate organ support in addition to initial medical treatment is necessary. Urgent or early gallbladder drainage is recommended. Elective cholecystectomy can be performed after the improvement of the acute inflammatory process.


Keywords  Acute cholangitis · Acute cholecystitis · Biliary drainage · Laparoscopic cholecystectomy · Guidelines

Introduction

This article describes strategies for the management of acute cholangitis and cholecystitis including initial medical treatment flowcharts. We established a flowchart for the diagnosis and treatment of acute cholangitis and cholecystitis as reported in the Tokyo Guidelines 2007 [1]. Flowcharts for the management of acute cholangitis and cholecystitis have been revised in the updated Tokyo Guidelines (TG13).

We consider that the primary purpose of the flowcharts is to allow clinicians to grasp, at a glance, the outline of the management strategy of the disease. Flowcharts have been colored for easy access and rapid understanding, and most of the treatment methods are included in the flowcharts to achieve their primary purpose.

Fig. 1 General guidance for the management of acute biliary inflammation/infection

General guidance for the management of acute cholangitis

The general guidance for the management of acute biliary inflammation/infection including acute cholangitis is presented in Fig. 1.

Clinical presentations

Clinical findings associated with acute cholangitis include abdominal pain, jaundice, fever (Charcot’s triad), and rigor. The triad was reported in 1887 by Charcot [2] as the indicators of hepatic fever and has been historically used as the generally accepted clinical findings of acute cholangitis. All three symptoms are observed in about 50–70 % of the patients with acute cholangitis [3–6]. Reynolds’ pentad—Charcot’s triad plus shock and decreased level of consciousness—were presented in 1959 when Reynolds and Dargan [7] defined acute obstructive cholangitis. Reynolds’ pentad is often referred to as the findings representing serious conditions, but shock and a decreased level of consciousness are only observed in less than 30 % of patients with acute cholangitis [3–6]. A history of biliary...
diseases such as gallstones, previous biliary procedures, or the placement of a biliary stent is very helpful when a diagnosis of acute cholangitis is suspected [1].

Blood test

The diagnosis of acute cholangitis requires the measurement of white blood cell count, C-reactive protein, and liver function test including alkaline phosphatase, GGT, AST, ALT, and bilirubin [8]. The assessment of the severity of the illness requires knowledge of the platelet count, blood urea nitrogen, creatinine, prothrombin time-international normalized ratio (PT-INR), albumin, and arterial blood gas analysis. Blood cultures are also helpful for selection of antimicrobial drugs [8–10]. Hyperamylasemia is a useful parameter for identifying complications such as choledocholithiasis causing biliary pancreatitis [11].

Diagnostic imaging

Abdominal ultrasound (US) and abdominal computerized tomography (CT) with intravenous contrast are very useful test procedures for evaluating patients with acute biliary tract disease. Abdominal US should be performed in all patients with suspected acute biliary inflammation/infection [1]. Ultrasonic examination has satisfactory diagnostic capabilities when performed not only by specialists but also by emergency physicians [12, 13]. The role of diagnostic imaging in acute cholangitis is to determine the presence of biliary obstruction, the level of obstruction, and the cause of the obstruction such as gallstones and/or biliary strictures [1]. The assessment should include US and CT. These studies complement each other and CT may yield better imaging of bile duct dilatation and pneumobilia.

Differential diagnosis

Diseases which should be differentiated from acute cholangitis are acute cholecystitis, liver abscess, gastric and duodenal ulcer, acute pancreatitis, acute hepatitis, and septicemia from other origins.

Q1. What is the initial medical treatment of acute cholangitis?

| On condition that biliary drainage is conducted during hospital stay as a rule, sufficient infusion, electrolyte correction, and antimicrobial and analgesic administration take place while fasting (recommendation 1, level C). |

Early treatment, while fasting as a rule, includes sufficient infusion, the administration of antimicrobial and analgesic agents, along with the monitoring of respiratory hemodynamic conditions in preparation for emergency drainage [1].

When acute cholangitis has become more severe, that is, if any one of the following signs is observed such as shock (reduced blood pressure), consciousness disturbance, acute lung injury, acute renal injury, hepatic injury, and disseminated intravascular coagulation (DIC) (decreased platelet count), emergency biliary drainage is carried out together with appropriate organ support (sufficient infusion and anti-microbial administration), and respiratory and circulatory management (artificial respiration, intubation, and use of vasopressors) [1].

Q2. Should the severe sepsis bundle be referred to for the early treatment of acute cholangitis accompanying severe sepsis?

The severe sepsis bundle should be referred to for the early treatment of acute cholangitis accompanying severe sepsis (recommendation 1, level B).

Acute cholangitis is frequently accompanied by sepsis. As for the early treatment of severe sepsis, there is a detailed description in “Surviving Sepsis Campaign Guidelines (SSCG)” published in 2004 and updated in 2008. To improve treatment results, a severe sepsis bundle (Table 1, http://www.ihi.org/knowledge/Pages/Changes/ImplementEffectiveGlucoseControl.aspx) has been presented in SSCG as the core part of the treatment for septic shock. However, there are reports of validation by several multi-institutional collaborative studies that have found a significant decrease in mortality rate in patients with a higher rate of compliance [14] or after the implementation of the severe sepsis bundle [15–17]. These studies include severe sepsis cases induced by a disease other than acute cholangitis [14–17]. However, the severe sepsis bundle should be referred to for the early treatment of acute cholangitis accompanying severe sepsis.

Flowchart for the management of acute cholangitis

A flowchart for the management of acute cholangitis is shown in Fig. 2. Treatment of acute cholangitis should be performed according to the severity grade of the patient. Biliary drainage and antimicrobial therapy are the two most important elements of treatment. When a diagnosis of acute cholangitis is determined based on the diagnostic criteria of
Acute cholangitis of TG13 [9], initial medical treatment including nil per os (NPO), intravenous fluid, antimicrobial therapy, and analgesia together with close monitoring of blood pressure, pulse, and urinary output should be initiated. Simultaneously, severity assessment of acute cholangitis should be conducted based on the severity assessment criteria for acute cholangitis of TG 13 [9] in which acute cholangitis is classified into Grade I (mild), Grade II (moderate), or Grade III (severe). Frequent reassessment is mandatory and patients may need to be reclassified into Grade I, II, or III based on the response to initial medical treatment. Appropriate treatment should be performed in accordance with the severity grade. Patients with acute cholangitis sometimes suffer simultaneously from acute cholecystitis. A treatment strategy for patients with both acute cholangitis and cholecystitis should be determined in consideration of the severity of those diseases and the surgical risk in patients.

Grade I (mild) acute cholangitis

Initial medical treatment including antimicrobial therapy may be sufficient. Biliary drainage is not required for most cases. However, for non-responders to initial medical treatment, biliary drainage should be considered. Endoscopic, percutaneous, or operative intervention for the etiology of acute cholangitis such as choledocholithiasis and pancreato-biliary malignancy may be performed after pre-intervention work-up. Treatment for etiology such as endoscopic sphincterotomy for choledocholithiasis might be performed simultaneously, if possible, with biliary drainage. Some patients who have

Table 1 Severe sepsis bundle, quoted from http://www.survivingsepsis.org/Bundles/Pages/default.aspx

<table>
<thead>
<tr>
<th>Diagnosis and Severity Assessment by TG13 Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I (Mild)</td>
</tr>
<tr>
<td>Antibiotics and General Supportive Care</td>
</tr>
</tbody>
</table>

Treatment According to Grade, According to Response, and According to Need for Additional Therapy

- Finish course of antibiotics
- Biliary Drainage
- Antibiotics
- Organ Support

Treatment for etiology if still needed
- (Endoscopic treatment, percutaneous treatment, or surgery)

† Performance of a blood culture should be taken into consideration before initiation of administration of antibiotics. A bile culture should be performed during biliary drainage.
† Principle of treatment for acute cholangitis consists of antimicrobial administration and biliary drainage including treatment for etiology. For patient with choledocholithiasis, treatment for etiology might be performed simultaneously, if possible, with biliary drainage.

Fig. 2 Flowchart for the management of acute cholangitis: TG13
developed postoperative cholangitis may require antimicrobial therapy only and generally do not require intervention.

Grade II (moderate) acute cholangitis

Early endoscopic or percutaneous drainage, or even emergency operative drainage with a T-tube, should be performed in patients with Grade II acute cholangitis. A definitive procedure should be performed to remove a cause of acute cholangitis after the patient’s general condition has improved and following pre-intervention work-up.

Grade III (severe) acute cholangitis

Patients with acute cholangitis accompanied by organ failure are classified as Grade III (severe) acute cholangitis. These patients require appropriate organ support such as ventilatory/circulatory management (non-invasive/invasive positive pressure ventilation and use of vasopressor, etc.). Urgent biliary drainage should be anticipated. When patients are stabilized with initial medical treatment and organ support, urgent (as soon as possible) endoscopic or percutaneous transhepatic biliary drainage or, according to the circumstances, an emergency operation with decompression of the bile duct with a T-tube should be performed. Definitive treatment for the cause of acute cholangitis including endoscopic, percutaneous, or operative intervention should be considered once the acute illness has resolved.

General guidance for the management of acute cholecystitis

The general guidance for the management of acute biliary inflammation/infection including acute cholecystitis is presented in Fig. 1.

Clinical presentations

Clinical symptoms of acute cholecystitis include abdominal pain (right upper abdominal pain), nausea, vomiting, and pyrexia [18–20]. The most typical symptom is right epigastric pain. Tenderness in the right upper abdomen, a palpable gallbladder, and Murphy’s sign are the characteristic findings of acute cholecystitis. A positive Murphy’s sign shows 79–96 % specificity [18, 20] for acute cholecystitis.

Blood test

There is no specific blood test for acute cholecystitis; however, the measurement of white blood cell count and C-reactive protein is very useful in confirming an inflammatory response [21]. The platelet count, bilirubin, blood urea nitrogen, creatinine, prothrombin time-international normalized ratio (PT-INR), and arterial blood gas analysis are useful in assessing the severity status of the patient [21].

Diagnostic imaging

Abdominal ultrasound (US) and abdominal computerized tomography (CT) with intravenous contrast are very helpful procedures for evaluating patients with acute biliary tract disease. Abdominal US should be performed in every patient with suspected acute biliary inflammation/infection [1]. Ultrasonic examination has satisfactory diagnostic capability when it is performed not only by specialists but also by emergency physicians [12, 13]. Characteristic findings of acute cholecystitis include the enlarged gallbladder, thickened gallbladder wall, gallbladder stones and/or debris in the gallbladder, sonographic Murphy’s sign, pericholecystic fluid, and pericholecystic abscess [21]. Sonographic Murphy’s sign is a reliable finding of acute cholecystitis showing about 90 % sensitivity and specificity [22, 23], which is higher than those of Murphy’s sign.

Differential diagnosis

Diseases which should be differentiated from acute cholecystitis are gastric and duodenal ulcer, hepatitis, pancreatitis, gallbladder cancer, hepatic abscess, Fitz-Hugh–Curtis syndrome, right lower lobar pneumonia, angina pectoris, myocardial infarction, and urinary infection.

Q3. What is the initial medical treatment of acute cholecystitis?

While considering indications for surgery and emergency drainage, sufficient infusion and electrolyte correction take place, and antimicrobial and analgesic agents are administered while fasting continuing the monitoring of respiratory and hemodynamics (recommendation 1, level C).

Early treatment, with fasting as a rule, includes sufficient infusion, the administration of antimicrobial and analgesic agents, along with the monitoring of respiratory hemodynamics in preparation for emergency surgery and drainage [1].

When any one of the following morbidities is observed: further aggravation of acute cholecystitis, shock (reduced blood pressure), consciousness disturbance, acute respiratory injury, acute renal injury, hepatic injury, and DIC (reduced platelet count), then appropriate organ support
(sufficient infusion and antimicrobial administration), and respiratory and circulatory management (artificial respiration, intubation, and use of vasopressors) are carried out together with emergency drainage or cholecystectomy [1].

There are many reports showing that remission can be achieved by conservative treatment only [24–26]. On the other hand, there is a report demonstrating that mild cases may not require antimicrobial agents; however, prophylactic administration should take place due to possible complications such as bacterial infection. Furthermore, there is a report that was unable to detect a difference in the positive rate of sonographic Murphy’s sign depending on the presence or absence of the use of analgesic agents [27]. The administration of analgesic agents should therefore be initiated in the early stage.

CQ4. Is the administration of NSAID for the attack of impacted stones gallstone attack effective for preventing acute cholecystitis?

| NSAID administration is effective for impacted gallstone attack for preventing acute cholecystitis (recommendation 1, level A). |

Administration of non-steroidal anti-inflammatory drugs (NSAIDs) for gallstone attack is effective in preventing acute cholecystitis, and they are also widely known as analgesic agents. A NSAID such as diclofenac is thus used for early treatment. According to a report of a double blind randomized controlled trial (RCT) that compared the use of NSAIDs (diclofenac 75 mg intramuscular injection) with placebo [28] or hyoscine 20 mg intramuscular injection [29] for cases of impacted gallstone attack, NSAIDs prevented progression of the disease to acute cholecystitis and also reduced pain. Although NSAIDs have been effective for the improvement of gallbladder function in cases with chronic cholecystitis, there is no report showing that the administration of NSAIDs has contributed to improving the course of cholecystitis after its acute onset [30].

Flowchart for the management of acute cholecystitis

A flowchart for the management of acute cholecystitis is shown in Fig. 3. The first-line treatment of acute cholecystitis is early or urgent cholecystectomy, with laparoscopic cholecystectomy as a preferred method. In high-risk patients, gallbladder drainage such as percutaneous transhepatic gallbladder drainage (PTGBD), percutaneous transhepatic gallbladder aspiration (PTGBA), and endoscopic nasobiliary gallbladder drainage (ENGBD) is an alternative therapy in patients who cannot safely undergo urgent/early cholecystectomy [31, 32]. When a diagnosis of acute cholecystitis is determined based on the diagnostic criteria of acute cholecystitis in TG13 [33], initial medical treatment including NPO, intravenous fluids, antibiotics, and analgesia, together with close monitoring of blood pressure, pulse, and urinary output should be initiated. Simultaneously, severity assessment of acute cholecystitis should be conducted based on the severity assessment criteria for the acute cholecystitis of TG13 [33], in which acute cholecystitis is classified into Grade I (mild), Grade II (moderate), or Grade III (severe). Assessment of the operative risk for comorbidities and the patient’s general status should also be evaluated in addition to the severity grade.

After resolution of acute inflammation with medical treatment and gallbladder drainage, it is desirable that cholecystectomy is performed to prevent recurrence. In surgically high-risk patients with cholecystolithiasis, medical support after percutaneous cholecystolithotomy should be considered [34–36]. In patients with acalculous cholecystitis, cholecystectomy is not always required since recurrence of acute acalculous cholecystitis after gallbladder drainage is rare [31, 37].

Grade I (mild) acute cholecystitis

Early laparoscopic cholecystectomy is the first-line treatment. In patients with surgical risk, observation (follow-up without cholecystectomy) after improvement with initial medical treatment could be indicated.

Grade II (moderate) acute cholecystitis

Grade II (moderate) acute cholecystitis is often accompanied by severe local inflammation. Therefore, surgeons should take the difficulty of cholecystectomy into consideration in selecting a treatment method. Elective cholecystectomy after the improvement of the acute inflammatory process is the first-line treatment. If a patient does not respond to initial medical treatment, urgent or early gallbladder drainage is required. Early laparoscopic cholecystectomy could be indicated if advanced laparoscopic techniques are available. Grade II (moderate) acute cholecystitis with serious local complications is an indication for urgent cholecystectomy and drainage.

Grade III (severe) acute cholecystitis

Grade III (severe) acute cholecystitis is accompanied by organ dysfunction. Appropriate organ support such as ventilatory/circulatory management (noninvasive/invasive positive pressure ventilation and use of vasopressors, etc.) in addition to initial medical treatment is necessary. Urgent or early gallbladder drainage should be performed. Elective
cholecystectomy may be performed after the improvement of acute illness has been achieved by gallbladder drainage.

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**Conflict of interest** None.

**References**

TG13 management bundles for acute cholangitis and cholecystitis

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Abstract Bundles that define mandatory items or procedures to be performed in clinical practice have been increasingly used in guidelines in recent years. Observance of bundles enables improvement of the prognosis of target diseases as well as guideline preparation. There were no bundles adopted in the Tokyo Guidelines 2007, but the updated Tokyo Guidelines 2013 (TG13) have adopted this useful tool. Items or procedures strongly recommended in clinical practice have been prepared in the practical guidelines and presented as management bundles. TG13 defined the mandatory items for the management of acute cholangitis and acute cholecystitis. Critical parts of the bundles in TG13 include diagnostic process, severity assessment, transfer of patients if necessary, therapeutic approach, and time course. Their observance should improve the prognosis of acute cholangitis and cholecystitis. When utilizing TG13 management bundles, further clinical research needs to be conducted to evaluate the effectiveness and outcomes of the bundles. It is also expected that the present report will lead to evidence construction and contribute to further updating of the Tokyo Guidelines.


Keywords Cholangitis bundle · Cholecystitis bundle
Introduction

A bundle is a group of therapies for a disease that, when implemented together, may result in better outcomes than if implemented individually. In recent years, bundles that define mandatory items or procedures to be performed in clinical practice have been increasingly used in guidelines [1]. Compliance with bundles results in the preparation of guidelines as well as an improved prognosis of targeted diseases arising from the use of the guidelines [2, 3]. Levy et al. [4] reported that data from 15,022 subjects at 165 sites were analyzed to determine compliance with bundle targets and association with hospital mortality, and compliance with the entire resuscitation bundle increased linearly from 10.9 % in the first site quarter to 31.3 % by the end of 2 years. Furthermore the odds ratio for mortality improved the longer a site was in the Surviving Sepsis Campaign, resulting in an adjusted absolute drop of 0.8 % per quarter and 5.4 % over 2 years.

Murata et al. [5, 6] examined a total of 60,842 patients with acute cholangitis using the Japanese national administrative database. This report demonstrated the improved prognosis of in-hospital mortality with odds ratio of 0.856 among patients who were managed with high compliance with the items of recommendation Grades A and B in Tokyo Guidelines 2007 (TG07) as compared with the patients who were low-compliance. This shows the importance of preparing bundles by setting the recommended items to be observed in the guidelines. Although TG07 did not prepare bundles at that time, the updated Tokyo Guidelines 2013 (TG13) have adopted the management bundles for acute cholangitis and cholecystitis. The care bundles are designed to be easily achievable and sustainable both to implement and to audit.

Furthermore, we made a checklist. We hope to use the acute cholangitis and cholecystitis bundle checklist to help track your organization’s compliance with implementing each element of these bundles.

Efficacy of the bundle

In the process of developing TG13, mandatory items or procedures to be included in the management bundles have been discussed and defined among the Tokyo Guidelines Revision Committee members. The bundles have been developed and finalized by obtaining consensus. Based on the recommendations in TG13, items which are expected to yield favorable treatment results are included in the bundles. To underscore the time course or timing of the performance of each item, management bundles for acute cholangitis and cholecystitis have been developed. A checklist has also been prepared to confirm compliance with the bundles.

The bundles such as sepsis bundle [7–9], ventilator bundle [10, 11] or central line bundle [12], when implemented together, may result in better outcomes than if implemented individually. Good prognosis is also reported in cases in which a bundle has been achieved, but this may show that those cases which have achieved a bundle are in such good condition as to enable achievement of a bundle.

However, the improvement in prognosis in patients achieved through education concerning bundles demonstrates that implementation of bundles and education concerning them have been useful [9, 13].

Controversial points and harmful effects of bundles

There are many problems to be solved for the spread and implementation of bundles. In the guidelines, even if useful items have been implemented, the prognosis in patients is not improved without common knowledge of management bundles among medical care workers [13]. Furthermore, it is not possible to put bundles into practice without sufficient manpower and equipment [14], which should be improved, if possible. If improvement is impossible, an alternative treatment should be provided or patients should be transferred to a medical facility where the contents of bundles can be put into practice [15].

There is also a concern that bundles are used not for the purpose of improving the prognosis in patients and increasing efficiency, but for limiting the contents of medical care to keep health care costs down. Furthermore,
failure to carry out the contents of bundles should not lead to lawsuits [15].

**Acute cholangitis management bundle (Table 1)**

Items in the cholangitis management bundle are described in Table 1. The content of every bundle is developed from the recommendation of TG13. The mandatory items or procedures to be included in the management bundles have been discussed and defined among the Tokyo Guidelines Revision Committee members. The diagnostic criteria and the severity assessment of acute cholangitis in TG13 was made based on the article of Kiriyama et al. [16].

**Acute cholecystitis management bundle (Table 2)**

Items in the cholecystitis management bundle are described in Table 2. The content of every bundle is classified into

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**Table 1** Management bundle of acute cholangitis

1. When acute cholangitis is suspected, diagnostic assessment is made using TG13 diagnostic criteria every 6–12 h
2. Abdominal X-ray (KUB) and abdominal US are carried out, followed by CT scan, MRI, MRCP and HIDA scan
3. Severity is repeatedly assessed using severity assessment criteria; at diagnosis, within 24 h after diagnosis, and during the time zone of 24–48 h
4. As soon as a diagnosis has been made, the initial treatment is provided. The treatment is as follows: sufficient fluids replacement, electrolyte compensation, and intravenous administration of analgesics and full dose of antimicrobial agents are provided
5. For patients with Grade I (mild), when no response to the initial treatment is observed within 24 h, biliary tract drainage is carried out immediately
6. For patients with Grade II (moderate), biliary tract drainage is immediately performed along with the initial treatment. If early drainage cannot be performed due to the lack of facilities or skilled personnel, transfer of the patient is considered
7. For patients with Grade III (severe), urgent biliary tract drainage is performed along with the initial treatment and general supportive care. If urgent drainage cannot be performed due to the lack of facilities or skilled personnel, transfer of the patient is considered
8. For patient with Grade III (severe), organ supports (noninvasive/invasive positive pressure ventilation, use of vasopressors and antimicrobial agents, etc.) are immediately performed
9. Blood culture and/or bile culture is performed for Grade II (moderate) and III (severe) patients
10. Treatment for etiology of acute cholangitis with endoscopic, percutaneous, or operative intervention is considered once acute illness has resolved. Cholecystectomy should be performed for cholecystolithiasis after acute cholangitis has resolved

**Table 2** Management bundle of acute cholecystitis

1. When acute cholecystitis is suspected, diagnostic assessment is made using TG13 diagnostic criteria every 6–12 h
2. Abdominal US is carried out, followed by HIDA scan and CT scan if needed to make the diagnosis
3. Severity is repeatedly assessed using severity assessment criteria; at diagnosis, within 24 h after diagnosis, and during the time zone of 24–48 h
4. Take that cholecystectomy is performed into consideration, as soon as a diagnosis has been made, the initial treatment takes place involving the replacement of sufficient fluid after fasting, electrolyte compensation, intravenous injection of analgesics and full dose antimicrobial agents
5. For patients with Grade I (mild), cholecystectomy at an early stage within 72 h of onset of symptoms is recommended
6. If conservative treatment patients with Grade I (mild) is selected and no response to the initial treatment is observed within 24 h, reconsider early cholecystectomy if still within 72 h of onset of symptoms or biliary tract drainage
7. For patients with Grade II (moderate), perform immediate biliary drainage or drainage if no early improvement (or cholecystectomy in experienced centers) along with the initial treatment
8. For patients with Grade II (moderate) and III (severe) at high surgical risk, biliary drainage is immediately carried out
9. Blood culture and/or bile culture is performed for Grade II (moderate) and III (severe) patients
10. Among patients with Grade II (moderate), for those with serious local complications including biliary peritonitis, pericholecystic abscess, liver abscess or for those with gallbladder torsion, emphysematous cholecystitis, gangrenous cholecystitis, and purulent cholecystitis, emergency surgery is conducted (open or laparoscopic depending on experience) along with the general supportive care of the patient. If surgery cannot be performed due to the lack of facilities or skilled personnel, transfer of the patient is considered
11. For patients with Grade III (severe) with jaundice and those in poor general conditions, emergency gallbladder drainage is considered with initial therapy with antibiotics and general support measures. For patients who are found to have gallbladder stones during biliary drainage, cholecystectomy is performed at after 3 month interval after the patient’s general conditions are improved

**KUB** kidney–ureter–bladder. **US** ultrasonography, **CT** computed tomography, **MRI** magnetic resonance imaging, **MRCP** magnetic resonance cholangiopancreatography, **HIDA** hepatobiliary iminodiacetic acid
Table 3  Acute cholangitis bundle checklist
☐ Repeat diagnosis every 6–12 h
☐ Diagnostic imaging X-ray (KUB), US, CT scan, MRI, MRCP, HIDA scan
☐ Severity assessment at diagnosis and within 24 h after a diagnosis
☐ Repeat severity assessment every 24 h
☐ Immediately start antibiotics administration and general supportive care
☐ Grade I (mild): carry out biliary drainage when no symptom improvement is observed within 24 h
☐ Grade II (moderate): carry out biliary drainage immediately
☐ Grade III (severe): conduct emergency biliary drainage and perform organ support
☐ Consider transfer when procedures are unavailable as above
☐ Grade II (moderate) and III (severe): blood culture and bile culture
☐ Consider surgical procedures to remove causes after biliary drainage and improvement of organ failure

Table 4  Acute cholecystitis bundle checklist
☐ Repeat diagnosis every 6–12 h
☐ Diagnostic imaging US, HIDA scan and CT scan
☐ Severity assessment at diagnosis and within 24 h after diagnosis
☐ Repeat severity assessment every 24 h
☐ Immediately initiate antibiotics administration and general supportive care
☐ Grade I (mild): Cholecystectomy at an early stage within 72 h of onset of symptoms
☐ Conservative treatment for Grade I (mild): Worsening condition or no improvement is in condition observed within 24 h. Reconsider early cholecystectomy if still within 72 h or biliary drainage (cholecystostomy)
☐ Grade II (moderate): Immediate biliary drainage or drainage if no early improvement (or cholecystectomy in experienced centers) along with the initial treatment*
☐ After drainage treatment for Grade II (moderate): Elective cholecystectomy after symptom improvement at after 3 month interval
☐ Poor local control** for Grade II (moderate): Emergency abdominal drainage and/or cholecystectomy in experienced centers
☐ Grade II (moderate) and III (severe) at high surgical risk: Immediately biliary drainage
☐ Grade II (moderate) and III (severe): Blood culture and/or bile culture
☐ Grade III (severe): Initiate therapy with antibiotics and general support measures. Conduct emergency biliary drainage as soon as stable
☐ After drainage treatment for Grade III (severe): Elective cholecystectomy after symptom improvement at after 3 month interval
☐ Consider transfer when procedures are unavailable as above

* see bundle No.4
**see bundle No.10

References
5. Murata A, Matsuda S, Kuvabara K, Fujino Y, Kubo T, Fujimori K, et al. Evaluation of compliance with the Tokyo Guidelines for the recommendation of TG13. The mandatory items or procedures to be included in the management bundles have been discussed and defined among the Tokyo Guidelines Revision Committee members. The diagnostic criteria and the severity assessment of acute cholecystitis in TG13 was made based on the article of Yokoe et al. [17].

Check list for the use of management bundles for acute cholangitis and cholecystitis (Tables 3, 4)

A check list is shown for the effective use of bundles. The use of this list for medical care ensures standards, and is thought to improve effectiveness of the bundles. These check lists, including procedures, laboratories, monitoring and interventions required, should be placed by the bedside.

Conclusions

Bundles consist of important items for the effective use of TG13. Compliance with the bundles is expected to improve the prognosis of acute cholangitis and acute cholecystitis. Reports from various facilities have demonstrated that improved prognosis is expected through the use of the Tokyo Guidelines for acute cholangitis and cholecystitis. Furthermore, good use of those reports will contribute to evidence construction and future revision of TG13.

Acknowledgments We would like to express our deep gratitude to the following organizations for their great support and guidance in the preparation of TG13: Japanese Society for Abdominal Emergency Medicine, Japan Biliary Association, Japan Society for Surgical Infection, and the Japanese Society of Hepato-Biliary-Pancreatic Surgery.

Conflict of interest None.
TG13 antimicrobial therapy for acute cholangitis and cholecystitis

Therapy with appropriate antimicrobial agents is an important component in the management of patients with acute cholangitis and/or acute cholecystitis. In the updated Tokyo Guidelines (TG13), we recommend antimicrobial agents that are suitable from a global perspective for management of these infections. These recommendations focus primarily on empirical therapy (presumptive therapy), provided before the infecting isolates are identified. Such therapy depends upon knowledge of both local microbial epidemiology and patient-specific factors that affect selection of appropriate agents. These patient-specific factors include prior contact with the health care system, and we separate community-acquired versus healthcare-associated infections because of the higher risk...
of resistance in the latter. Selection of agents for community-acquired infections is also recommended on the basis of severity (grades I–III).


**Keywords** Acute cholangitis · Acute cholecystitis · Antimicrobial therapy · Treatment guidelines · Biliary tract infection

**Introduction**

Acute cholangitis and cholecystitis are common conditions that may result in progressively severe infection, particularly in debilitated hosts. Epidemiology and risk factors for acute cholangitis and cholecystitis are provided in a separated section of “TG13: Current terminology, etiology, and epidemiology of acute cholangitis and cholecystitis.” The primary goal of antimicrobial therapy in acute cholangitis and cholecystitis is to limit both the systemic septic response and local inflammation, to prevent surgical site infections in the superficial wound, fascia, or organ space, and to prevent intrahepatic abscess formation [1].

In acute cholangitis, drainage of the obstructed biliary tree (termed source control) was recognized as the mainstay of therapy long before the introduction of antimicrobial agents [1]. An additional role of antimicrobial therapy, allowing delay in operation until patients are more physiologically stable, was initially defined by Boey and Way [2]. They retrospectively reviewed 99 consecutive patients with acute cholangitis, and reported that 53 % of their patients who responded well to antimicrobial therapy were therefore given elective instead of emergency operation [1, 2].

The role of antimicrobial therapy in the broad range of diseases subsumed under the term “acute cholecystitis” also varies with severity and pathology. In early and non-severe cases, it is not obvious that bacteria play a significant role in the pathology encountered. In these patients, antimicrobial therapy is at best prophylactic, preventing progression to infection. In other cases, with clinical findings of a systemic inflammatory response, antimicrobial therapy is therapeutic, and treatment may be required until the gallbladder is removed.

**Rationale for changes in these guidelines**

Five years have passed since the Tokyo Guidelines were published in 2007, and it is now referred to as TG07 [3, 4]. During the last five years, there have been several developments in the management of biliary tract infections. For antimicrobial therapy, other guideline sources for biliary tract infections have been revised. These include the Surviving Sepsis Campaign 2008 [5] and treatment guidelines for complicated intra-abdominal infections developed by the Surgical Infection Society of North America (SIS-NA) and the Infectious Diseases Society of America (IDSA) 2010 [6]. Additionally, new agents and dosing regimens have been approved, including higher dose regimens for piperacillin/tazobactam, meropenem, levofloxacin and doripenem. The issues of pharmacokinetics and pharmacodynamics of antimicrobial agents have been clarified [3, 4]. Since the release of TG07 [3, 4], the emergence of antimicrobial resistance among clinical isolates of Enterobacteriaceae from patients with community-acquired intra-abdominal infections has been more widely reported [7–14]; in particular, antimicrobial resistance in Gram-negative bacilli driven by the appearance of extended-spectrum β-lactamases (ESBL) and carbapenemases (i.e., metallo-β-lactamase and non-metallo-β-lactamase) [15–19]. Finally, in the updated Tokyo Guidelines (TG13), both the diagnostic and severity criteria for acute cholangitis and cholecystitis have been revised and recommendations for antimicrobial therapy are reconsidered against this new structure.

There are new topics dealt with in these guidelines. We now make specific recommendations for antimicrobial therapy of healthcare-associated biliary infections. This was prompted by recognition of the increasing number of elderly patients with multiple medical problems exposed to the health care system and thereby at risk of acquiring resistant organisms [14]. In addition, there are several agents that are no longer recommended by the SIS-NA/IDSA 2010 guidelines [6]. We also clarify concerns regarding the importance (or lack thereof) of biliary penetration. We also now address prophylaxis for elective endoscopic retrograde cholangiopancreatography (ERCP).

**Background**

The bacteria commonly found in biliary tract infections are well known, and are presented in Tables 1 and 2 [3, 4, 20–31]. Antimicrobial therapy largely depends on local antimicrobial susceptibility data. In the international guidelines for acute cholangitis and cholecystitis (TG13), a framework for selecting antimicrobial agents will be provided, with class-based definitions of appropriate therapy. Listed agents in the guideline are appropriate for use, and recommendations for modification based upon the local microbiological findings, referred to as antibiogram, are made.

**Decision process**

A systematic literature review was performed using PubMed from January 1, 2005 to May 15, 2012. All references were searched with the keywords “Acute cholangitis” AND “Antibiotics OR Antimicrobial therapy,” and “Acute
cholecystitis” AND “Antibiotics OR Antimicrobial therapy” among human studies. Sixty-five and 122 articles were found, respectively. These references were further narrowed using keywords “Clinical trials” and “Randomized trials.” Literature cited in the TG07 was also reviewed and integrated for revision. If there were few data and few new developments on clinical questions addressed since 2005, a consensus process was used by the members of the Tokyo Guidelines Revision Committee after consultations with internationally recognized experts.

The structure of recommendations for selecting antimicrobial agents has been revised. Antimicrobial agents appropriate for initial therapy (empirical therapy or presumptive therapy) for various grades of severity of biliary tract infections have been developed. Table 3 lists antimicrobial agents appropriate for use for the treatment of patients with both community-acquired and healthcare-associated cholangitis and cholecystitis.

### Clinical questions

Clinically relevant questions are provided with brief answers and explanations below.

**Q1. What specimen should be sent for culture to identify the causative organisms in acute cholangitis and cholecystitis?**

- Bile cultures should be obtained at the beginning of any procedure performed. Gallbladder bile should be sent for culture in all cases of acute cholecystitis excepting those with grade I severity (recommendation 1, level C).
- We suggest cultures of bile and tissue when perforation, emphysematous changes, or necrosis of gallbladder are noted during cholecystectomy (recommendation 2, level D).
- Blood cultures are not routinely recommended for grade I community-acquired acute cholecystitis (recommendation 2, level D).

Identifying the causative organism(s) is an essential step in the management of acute biliary infections. Positive rates of bile cultures range from 59 to 93 % for acute cholangitis [3, 4, 20–27], and positive rates of either bile or gallbladder cultures range from 29 to 54 % for acute cholecystitis [3, 4, 20–27]. In a recent study which utilized the TG07 diagnostic classification, positive rates of bile cultures among patients with cholangitis were 67 % (66 of 98 patients) and 33 % (32 of 98) without [27]. Table 1 shows common microbial isolates from bile cultures among patients with acute biliary infections [3, 4, 20–27].

<table>
<thead>
<tr>
<th>Isolated microorganisms from bile cultures</th>
<th>Proportions of isolated organisms (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative organisms</td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>31–44</td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
<td>9–20</td>
</tr>
<tr>
<td><em>Pseudomonas</em></td>
<td>0.5–19</td>
</tr>
<tr>
<td><em>Enterobacter</em></td>
<td>5–9</td>
</tr>
<tr>
<td><em>Acinetobacter</em></td>
<td>–</td>
</tr>
<tr>
<td><em>Citrobacter</em></td>
<td>–</td>
</tr>
<tr>
<td>Gram-positive organisms</td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>3–34</td>
</tr>
<tr>
<td><em>Streptococcus</em></td>
<td>2–10</td>
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<tr>
<td><em>Staphylococcus</em></td>
<td>0 a</td>
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<tr>
<td>Anaerobes</td>
<td>4–20</td>
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<tr>
<td>Others</td>
<td>–</td>
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</tbody>
</table>

### Table 1 Common microorganisms isolated from bile cultures among patients with acute biliary infections

<table>
<thead>
<tr>
<th>Isolated microorganisms from bile cultures</th>
<th>Proportions of isolated organisms (%)</th>
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<tbody>
<tr>
<td>Gram-negative organisms</td>
<td></td>
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<tr>
<td><em>Escherichia coli</em></td>
<td>35–62</td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
<td>12–28</td>
</tr>
<tr>
<td><em>Pseudomonas</em></td>
<td>4–14</td>
</tr>
<tr>
<td><em>Enterobacter</em></td>
<td>2–7</td>
</tr>
<tr>
<td><em>Acinetobacter</em></td>
<td>3</td>
</tr>
<tr>
<td><em>Citrobacter</em></td>
<td>2–6</td>
</tr>
<tr>
<td>Gram-positive organisms</td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>10–23</td>
</tr>
<tr>
<td><em>Streptococcus</em></td>
<td>6–9</td>
</tr>
<tr>
<td><em>Staphylococcus</em></td>
<td>2</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Isolated microorganisms from blood cultures</th>
<th>Proportions of isolates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-acquired infections a</td>
<td>Healthcare-associated infections b</td>
</tr>
<tr>
<td>Gram-negative organisms</td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>35–62 23</td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
<td>12–28 16</td>
</tr>
<tr>
<td><em>Pseudomonas</em></td>
<td>4–14 17</td>
</tr>
<tr>
<td><em>Enterobacter</em></td>
<td>2–7 7</td>
</tr>
<tr>
<td><em>Acinetobacter</em></td>
<td>3 7</td>
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<tr>
<td><em>Citrobacter</em></td>
<td>2–6 5</td>
</tr>
<tr>
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<td></td>
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<tr>
<td><em>Enterococcus</em></td>
<td>10–23 20</td>
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<td><em>Streptococcus</em></td>
<td>6–9 5</td>
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<tr>
<td><em>Staphylococcus</em></td>
<td>2 4</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>1 2</td>
</tr>
<tr>
<td>Others</td>
<td>17 11</td>
</tr>
</tbody>
</table>

a The data are from references [14, 28–30]
b The data are from reference [14]
Table 3: Antimicrobial recommendations for acute biliary infections

<table>
<thead>
<tr>
<th>Severity</th>
<th>Antimicrobial agents</th>
<th>Community-acquired biliary infections</th>
<th>Healthcare-associated biliary infections</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Grade I</td>
<td>Cholangitis</td>
</tr>
<tr>
<td></td>
<td>Penicillin-based therapy</td>
<td>Ampicillin/sulbactam&lt;sup&gt;b&lt;/sup&gt; is not recommended without an aminoglycoside</td>
<td>Ampicillin/sulbactam&lt;sup&gt;b&lt;/sup&gt; is not recommended without an aminoglycoside</td>
</tr>
<tr>
<td></td>
<td>Cephalosporin-based therapy</td>
<td>Cefazolin&lt;sup&gt;a&lt;/sup&gt;, or cefotiam&lt;sup&gt;a&lt;/sup&gt;, or cefuroxime&lt;sup&gt;c&lt;/sup&gt;, or ceftriaxone, or cefotaxime ± metronidazole&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Cefazolin&lt;sup&gt;a&lt;/sup&gt;, or cefotiam&lt;sup&gt;a&lt;/sup&gt;, or cefuroxime&lt;sup&gt;c&lt;/sup&gt;, or ceftriaxone, or cefotaxime ± metronidazole&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Carbapenem-based therapy</td>
<td>Ertapenem</td>
<td>Ertapenem</td>
</tr>
<tr>
<td></td>
<td>Monobactam-based therapy</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolone-based therapy&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Ciprofloxacin, or levofloxacin, or pazufloxacin ± metronidazole&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Ciprofloxacin, or levofloxacin, or pazufloxacin ± metronidazole&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moxifloxacin</td>
<td>Moxifloxacin</td>
</tr>
</tbody>
</table>

<sup>a</sup> Local antimicrobial susceptibility patterns (antibiogram) should be considered for use.
<sup>b</sup> Ampicillin/sulbactam has little activity left against Escherichia coli. It is removed from the North American guidelines [6].
<sup>c</sup> Fluoroquinolone use is recommended if the susceptibility of cultured isolates is known or for patients with β-lactam allergies. Many extended-spectrum β-lactamase (ESBL)-producing Gram-negative isolates are fluoroquinolone-resistant.
<sup>d</sup> Anti-anaerobic therapy, including use of metronidazole, tinidazole, or clindamycin, is warranted if a biliary-enteric anastomosis is present. The carbapenems, piperacillin/tazobactam, ampicillin/sulbactam, cefmetazole, cefoxitin, flomoxef, and cefoperazone/sulbactam have sufficient anti-anerobic activity for this situation.
<sup>e</sup> Vancomycin is recommended to cover Enterococcus spp. for grade III community-acquired acute cholangitis and cholecystitis, and healthcare-associated acute biliary infections. Linezolid or daptomycin is recommended if vancomycin-resistant Enterococcus (VRE) is known to be colonizing the patient, if previous treatment included vancomycin, and/or if the organism is common in the community.
to range from 7.7 to 15.8 % [28, 31]. Table 2 shows the most recently reported microbial isolates from patients with bacteremic biliary tract infections [14, 28–30].

There is a lack of clinical trials examining the benefit of blood cultures in patients with acute biliary tract infections. Most of the bacteremic isolates reported (Table 2) are organisms that do not form vegetations on normal cardiac valves nor miliary abscesses. Their intravascular presence does not lead to an extension of therapy or selection of multidrug regimens. We therefore recommend such cultures be taken only in high-severity infections when such results might mandate changes in therapy [5]. Blood cultures are not routinely recommended for grade I community-acquired acute cholecystitis (level D).

The SIS-NA/IDSA 2010 guidelines recommended against routine blood cultures for community-acquired intra-abdominal infections, since the results do not change the management and outcomes [6]. This is in part driven by a study of the clinical impact of blood cultures taken in the emergency department [32]. In this retrospective study, 1,062 blood cultures were obtained during the study period, of which 92 (9 %) were positive. Of the positive blood cultures, 52 (5 %) were true positive, and only 18 (1.6 %) resulted in altered management.

Q2. What considerations should be taken when selecting antimicrobial agents for the treatment of acute cholangitis and cholecystitis?

- When selecting antimicrobial agents, targeted organisms, pharmacokinetics and pharmacodynamics, local antibiogram, a history of antimicrobial usage, renal and hepatic function, and a history of allergies and other adverse events should be considered (recommendation 1, level D).
- We suggest anaerobic therapy if a biliary-enteric anastomosis is present (recommendation 2, level C).

There are multiple factors to consider in selecting empiric antimicrobial agents. These include targeted organisms, local epidemiology and susceptibility data (antibiogram), alignment of in-vitro activity (or spectrum) of the agents with these local data, characteristics of the agents such as pharmacokinetics and pharmacodynamics, and toxicities, renal and hepatic function, and any history of allergies and other adverse events with antimicrobial agents [3, 4, 20–27]. A history of antimicrobial usage is important because recent (<6 months) antimicrobial therapy greatly increases the risk of resistance among isolated organisms.

Before dosing antimicrobial agents, renal function should be estimated with the commonly used equation: Serum creatinine = (140 – age) [optimum body weight (kg)]/72 × serum creatinine (mg/dl) [3, 4, 33]. Individual dosage adjustments for altered renal and hepatic function are available in several recent publications [34, 35]. Consultation with a clinical pharmacist is recommended if there are concerns.

Regarding the timing of therapy, it should be initiated as soon as the diagnosis of biliary infection is suspected. For patients in septic shock, antimicrobials should be administered within 1 h of recognition [5]. For other patients, as long as 4 h may be spent obtaining definitive diagnostic studies prior to beginning antimicrobial therapy. Antimicrobial therapy should definitely be started before any procedure, either percutaneous, endoscopic, or operative, is performed. In addition, anaerobic therapy is appropriate if a biliary-enteric anastomosis is present (level C) [6].

Selected newer agents

Moxifloxacin has been investigated for intra-abdominal infections in several randomized studies [36–39]. It was demonstrated that moxifloxacin is safe, well-tolerated, and non-inferior to the comparators, such as ceftriaxone plus metronidazole [37], or piperacillin/tazobactam followed by amoxicillin/clavulanic acid [39]. This study was conducted prior to the appearance of ESBL-mediated resistance [40]. There are few data specifically regarding the treatment of acute cholangitis or cholecystitis, and resistance rates of E. coli and other common Enterobacteriaceae to fluoroquinolones have risen [7–14].

Tigecycline was under clinical trials for approval during preparation of the manuscript, and is now approved for clinical use in Japan. Tigecycline has in-vitro activity against a wide range of clinically significant Gram-positive and Gram-negative bacteria [41]. These include multidrug-resistant Gram-positive cocci such as methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus spp. For Gram-negative bacilli, ESBL-producing Enterobacteriaceae are susceptible, as are most anaerobes. Tigecycline has no activity against Pseudomonas aeruginosa. Tigecycline has been investigated for skin and soft tissue infections and complicated intra-abdominal infections [41]. Tigecycline causes nausea and vomiting in approximately 10–20 % of patients, and is dose-related. This limits the dose that can be routinely administered and suggests only a secondary role for this agent, in the event of unusual pathogens or allergy to other classes of antimicrobial agents. Recent meta-analyses have demonstrated an increased mortality rate and treatment failure rate in randomized trials with this agent [42].

Antimicrobial agents appropriate for use in the management of community-acquired acute cholangitis and cholecystitis

Table 3 summarizes antimicrobial recommendations. It should be kept in mind that in the treatment of cholangitis,
source control (i.e., drainage) is an essential part of management. The indications and timing for drainage are provided in the severity and flowchart of the management sections regarding acute cholangitis. Since 2005, there have been no randomized clinical trials of antimicrobial therapy for community-acquired acute cholangitis and/or acute cholecystitis. There have been multiple reports on clinical isolates with multiple drug resistance from intra-abdominal infections worldwide, and biliary infections in particular [7–14, 40]. Recommendations for antimicrobial therapy are based primarily upon extrapolations of microbiological efficacy and behavior of these agents against the more susceptible isolates treated in the clinical trials cited [36–39, 43–49]. Some concerns about this approach to defining efficacy against resistant isolates has been raised [50]. The use of severity of illness as a guide to antimicrobial agent selection has been questioned in the face of the increasing numbers of ESBL-producing E. coli and Klebsiella in the community. These organisms are not reliably susceptible to cephaplosporins, penicillin derivatives, or fluoroquinolones. Previous guidelines have recommended that if more than 10–20 % of community isolates of E. coli are so resistant, then empiric coverage should be provided for these organisms until susceptibility data demonstrates sensitivity to narrower spectrum agents. Carbapenems, piperacillin/tazobactam, tigecycline, or amikacin may also be used to treat these isolates [6]. For grade III community-acquired acute cholangitis and cholecystitis, agents with anti-pseudomonal activities are recommended as initial therapy (empirical therapy) until causative organisms are identified. Pseudomonas aeruginosa is present in approximately 20 % of recent series [14, 27], and is a known virulent pathogen. Failure to empirically cover this organism in critically ill patients may result in excess mortality.

Enterococcus spp. is another important pathogen for consideration in patients with grade III community-acquired acute cholangitis and cholecystitis. Vancomycin is recommended to cover Enterococcus spp. for patients with grade III community-acquired acute cholangitis and/or cholecystitis, until the results of cultures are available. Ampicillin can be used if isolated strains of Enterococcus spp. are susceptible to ampicillin. Ampicillin covers most of the strains of Enterococcus faecalis from community-acquired infections in general. For Enterococcus faecium, vancomycin is the drug of choice for empirical therapy. However, in many hospitals, vancomycin-resistant Enterococcus spp., both E. faecium and E. faecalis, have emerged as important causes of infection. Treatment for these organisms requires either linezolid or daptomycin. Surgeons and other physicians making treatment decisions for patients with healthcare-associated infections should be aware of the frequency of these isolates in their hospital and unit. Then, regarding infrequently isolated anaerobes such as the Bacteroides fragilis group, we suggest to cover these organisms empirically when a biliary-enteric anastomosis is present (level C) [6]. For grade I and II community-acquired cholangitis and cholecystitis, Table 3 shows the agents appropriate for use. Of note, the intravenous formulation of metronidazole has not been approved in Japan. As a result, clindamycin is one of the alternatives where intravenous metronidazole is not available. Clindamycin resistance among Bacteroides spp. is significant and the use of clindamycin is no longer recommended in other intra-abdominal infections [6]. Cefoxitin, cefmetazole, flomoxef, and cefoperazone/sulbactam are the agents in cephalosporins that have activities against Bacteroides spp. Cefoxitin is no longer recommended by the SIS-NA/IDSA 2010 guidelines due to the high prevalence of resistance among Bacteroides spp. [6]. Local availability of agents as well as local susceptibility results are emphasized when choosing empirical therapy.

Table 4 summarizes antimicrobial agents with high prevalence of resistance among Enterobacteriaceae [7–14]. Ampicillin/sulbactam is one of the most frequently used agents for intra-abdominal infections. Nonetheless, the activity of ampicillin/sulbactam against E. coli, with or without ESBLs, has fallen to levels that prevent a recommendation for its use. In the TG13, ampicillin/sulbactam alone is not recommended as empirical therapy if the local susceptibility is <80 %. It is reasonable to use ampicillin/sulbactam as definitive therapy when the susceptibility of this agent is proven. Ampicillin/sulbactam may be used if an aminoglycoside is combined until susceptibility testing results are available.

Table 4 Antimicrobial agents with high prevalence of resistance among Enterobacteriaceae

<table>
<thead>
<tr>
<th>Antimicrobial class</th>
<th>Antimicrobial agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>Ampicillin/sulbactam</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Cefazolin</td>
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<tr>
<td></td>
<td>Cefuroxime</td>
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<tr>
<td></td>
<td>Cefotiam</td>
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<tr>
<td></td>
<td>Cefoxitin</td>
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<tr>
<td></td>
<td>Cefmetazole</td>
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<tr>
<td></td>
<td>Flomoxef</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Ceftriaxone a or cefotaxime a</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
</tr>
</tbody>
</table>

References [4–11]

a This resistance indicates the global spread of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae
Fluoroquinolone use is only recommended if the susceptibility of cultured isolates is known since antimicrobial resistance has been increasing significantly [7–14]. This agent can also be used as an alternative agent for patients with β-lactam allergies.

Antimicrobial agents appropriate for use in the management of healthcare-associated acute cholangitis and cholecystitis

There is no evidence to support any agent as optimal treatment of healthcare-associated acute cholangitis and cholecystitis. The principles of empirical therapy of healthcare-associated infections include using agents with anti-pseudomonal activity until definitive causative organisms are found. This paradigm is now expanded to include empirical coverage for ESBL-producing Gram-negative organisms based on local microbiological findings (local antibiogram). Table 3 shows empirical agents (presumptive therapy) for healthcare-associated acute cholangitis and cholecystitis. Vancomycin is recommended when patients are colonized with resistant Gram-positive bacteria such as methicillin-resistant Staphylococcus aureus and/or Enterococcus spp. or when these multidrug-resistant Gram-positives are of concern. Staphylococcus aureus is not as common an isolate for acute biliary infections as Enterococcus spp. Vancomycin-resistant Enterococcus (VRE) should be covered empirically with linezolid or daptomycin if this organism is known to be colonizing the patient, if previous treatment included vancomycin, and/or if the organism is common in the community.

Regarding anaerobes such as the Bacteroides fragilis group, we suggest to cover these organisms empirically in the presence of a biliary-enteric anastomosis (level C) [6].

Is it necessary for agents used in acute biliary infections to be concentrated in bile?

Historically, biliary penetration of agents has been considered in the selection of antimicrobial agents. However, there is considerable laboratory and clinical evidence that as obstruction occurs, secretion of antimicrobial agents into bile stops [1]. Well-designed randomized clinical trials comparing agents with or without good biliary penetration are needed to determine the clinical relevance and significance of biliary penetration in treating acute biliary infections.

How should highly resistant causative organisms be managed in treating acute cholangitis and cholecystitis?

The major microbiological phenomenon of the last decade has been the emergence of novel β-lactamase-mediated resistance mechanisms in Enterobacteriaceae. These have been seen in intra-abdominal infections worldwide [7–19, 27]. These organisms have moved into many communities, and are now seen increasingly in community-acquired infections such as cholangitis and cholecystitis. The frequency of ESBL-producing E. coli and Klebsiella spp. has reached the point in some countries where decisions regarding empirical therapy must be guided by their prevalence. ESBL-producing E. coli is highly susceptible to carbapenems and to tigecycline. In some communities, highly resistant Klebsiella spp. and E. coli with carbapenemases are now seen [51–54]. The widely accepted rule for empirical therapy is that resistant organisms occurring in more than 10–20 % of patients should be treated. Colistin is the salvage agent for the above multidrug-resistant Gram-negative bacilli epidemic strains [40, 54]. This agent is toxic, dosing is uncertain, and its use should involve consultation with infectious disease specialists [40].

In the SIS-NA/IDSA 2010 guidelines [6], antimicrobial agents as empirical therapy for healthcare-associated intra-abdominal infections were given. In the guidelines, carbapenems, piperacillin/tazobactam, and ceftazidime or cefepime, each combined with metronidazole, have been recommended when the prevalence of resistant Pseudomonas aeruginosa, ESBL-producing Enterobacteriaceae, Acinetobacter or other multidrug-resistant Gram-negative bacilli is less than 20 %. For ESBL-producing Enterobacteriaceae, carbapenems, piperacillin/tazobactam, and aminoglycosides are recommended. For Pseudomonas aeruginosa, if the prevalence of resistance to ceftazidime is more than 20 %, carbapenems, piperacillin/tazobactam, and aminoglycosides are recommended. Even with this guide, selecting appropriate agents for antimicrobial stewardship is often difficult.

Q3. What are the special concerns for community-acquired acute cholecystitis in management with antimicrobial agents?

- When cholecystectomy is performed, antimicrobial therapy can be stopped within 24 hours since the source of infection is controlled (recommendation 2, level C).
- Grade II or Grade III acute cholecystitis should be treated with antimicrobial therapy even after cholecystectomy is performed (recommendation 1, level D).
- In patients with pericholecystic abscesses or perforation of the gallbladder, treatment with an antimicrobial regimen as listed in Table 3 is recommended. Therapy should be continued until the patient is afebrile, with a normalized white count, and without abdominal findings (recommendation 1, level D).

In most cases, cholecystectomy removes the infection, and little if any infected tissue remains. Under these circumstances, there is no benefit to extending antimicrobial therapy beyond 24 h.
Recent randomized clinical trials for antimicrobial therapy of acute cholecystitis are limited [43, 46–48]. In these randomized studies, comparisons were made such as ampicillin plus tobramycin versus piperacillin or cefoperazone, pefloxacin versus ampicillin and gentamicin, and cefepime versus mezlocillin plus gentamicin [4, 43, 46, 48]. There were no significant differences between the agents compared. In the TG13, the agents considered as appropriate therapy, and detailed in Table 3, have all been utilized in randomized controlled trials of intra-abdominal infections. These studies included patients with pathologically advanced cholecystitis (abscess or perforation). Table 3 is provided for both community-acquired and healthcare-associated acute cholecystitis.

Antimicrobial therapy after susceptibility testing results are available

Once susceptibility testing results of causative microorganisms are available, specific therapy (or definitive therapy) should be offered. This process is called de-escalation [5]. Agents in Table 4 can be used safely once the susceptibility is proven.

Duration of treatment of patients with clinical and laboratory success

The optimal duration of antimicrobial therapy for community-acquired and healthcare-associated acute cholangitis and cholecystitis has not been determined in well-designed randomized controlled studies. Whether the source of infection (i.e., biliary obstruction) is well controlled or not is critical in determining the duration of therapy. In addition, recent technological advances for biliary drainage have significantly affected the overall management strategies for at least the last two decades.

In the SIS-NA/IDSA 2010 guidelines, the recommended duration of antimicrobial therapy for complicated intra-abdominal infections is 4–7 days once the source of infection is controlled [6]. Since there are very few data available for the duration of either community-acquired or healthcare-associated acute cholangitis and cholecystitis, Table 5 was developed to guide the duration of antimicrobial therapy as expert opinion. When bacteremia with Gram-positive bacteria such as Enterococcus spp. and Streptococcus spp. is present, it is prudent to offer antimicrobial therapy for two weeks since these organisms are well known to cause infective endocarditis.

Conversion to oral antimicrobial agents

Patients with acute cholangitis and cholecystitis who can tolerate oral feeding may be treated with oral therapy [55]. Depending on the susceptibility patterns of the organisms identified, oral antimicrobial agents such as fluoroquinolones (ciprofloxacin, levofloxacin, or moxifloxacin), amoxicillin/clavulanic acid, or cephalosporins may also be used. Table 6 lists commonly used oral antimicrobial agents with good bioavailabilities.

What is the optimal prophylactic agent before elective endoscopic retrograde cholangiopancreatography (ERCP)?

A Cochrane meta-analysis examining the benefits of antibiotic prophylaxis for elective ERCP has been performed, and found benefit to the practice [56]. The international guidelines on prophylaxis with endoscopy indicated that

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**Table 5** Recommended duration of antimicrobial therapy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Durability of infection</th>
<th>Severity of Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholecystitis</td>
<td></td>
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<tr>
<td>Cholangitis</td>
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<tr>
<td>Antimicrobial therapy can be</td>
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<tr>
<td>discontinued within 24 h after</td>
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<tr>
<td>cholecystectomy is performed</td>
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<tr>
<td>Once source of infection is</td>
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<tr>
<td>controlled, duration of 4–7 days is</td>
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<tr>
<td>recommended</td>
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<tr>
<td>If bacteremia with Gram-positive</td>
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<tr>
<td>cocci such as <em>Enterococcus</em> spp.,</td>
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<tr>
<td><em>Streptococcus</em> spp. is present,</td>
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<tr>
<td>minimum duration of 2 weeks is</td>
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<tr>
<td>recommended</td>
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<tr>
<td>If residual stones or obstruction of</td>
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<tr>
<td>the bile tract are present,</td>
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<tr>
<td>treatment should be</td>
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<td>continued until these anatomical</td>
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<tr>
<td>problems are resolved</td>
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</tr>
</tbody>
</table>

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**Table 6** Commonly used oral antimicrobial agents

<table>
<thead>
<tr>
<th>Oral antimicrobial agents</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>High</td>
</tr>
<tr>
<td>Amoxicillin/clavulanic</td>
<td>High</td>
</tr>
<tr>
<td>Acid cephalosporins</td>
<td>High</td>
</tr>
</tbody>
</table>

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prophylaxis with ERCP is recommended [57]. As consensus statements, the guidelines [57] recommended the standard prophylaxis regimen to prevent infective endocarditis. The regimen includes amoxicillin or clindamycin orally, or ampicillin or cefazolin as intravenous agents, and vancomycin for patients with β-lactam allergies to prevent infective endocarditis. However, the regimens for preventing cholangitis and bacteremia due to obstructive biliary tract were not included.

Recent meta-analyses [56, 58] had conflicting conclusions regarding the effectiveness of prophylactic therapy before elective ERCP. Bai et al. concluded that prophylactic agents cannot prevent cholangitis [58], while a Cochrane review indicated that prophylactic antimicrobial therapy before elective ERCP reduces the incidence of bacteremia [relative risk (RR) 0.50], cholangitis (RR 0.54), and pancreatitis (RR 0.54) [56]. However, overall mortality was not reduced with prophylaxis before elective ERCP [RR 1.33, confidence interval (CI) 0.32–5.44]. In this review, the numbers needed to treat (NNT) to prevent bacteremia (NNT = 11) and cholangitis (NNT = 38) were also demonstrated. The Cochrane review concluded that further studies are needed, including randomized placebo-controlled studies, to investigate the effectiveness of prophylaxis for elective ERCP with low risk of bias, randomized comparison of the timing of administration of prophylaxis (before vs. during or after ERCP), and randomized head-to-head comparison of antimicrobial agents as prophylactic therapy with elective ERCP [56].

Antimicrobial agents investigated with elective ERCP include minocycline orally [59], piperacillin [60, 61], clindamycin plus gentamicin [62], cefuroxime [63], cefotaxime [64, 65], and ceftazidime [66].

In the TG13, antimicrobial prophylactic agents appropriate for use in preventing cholangitis or bacteremia due to biliary tract obstruction are provided on a consensus basis. Table 7 lists those agents. Cefazolin or other narrower-spectrum cephalosporins can be used as prophylactic agents. Cefazolin is one of the agents for preventing infective endocarditis with endoscopy and a convenient agent to be used to prevent both endocarditis and cholangitis. Piperacillin is one of the anti-pseudomonal agents that have been studied as a prophylactic agent for elective ERCP [60, 61]. Given the emergence of resistance among Gram-negative organisms worldwide, including ESBL-producing strains [7–14, 27], we recommend anti-pseudomonal agents such as piperacillin or piperacillin/tazobactam listed in Table 7.

Use of antibiotic irrigation

There has been continuing interest in irrigation of surgical fields with antimicrobial agents, and the subject has recently been reviewed [67]. The authors concluded that topical antimicrobial agents are clearly effective in reducing wound infections and may be as effective as the use of systemic antimicrobial agents. The combined use of systemic and topical antimicrobial agents may have additive effects, but this is lessened if the same agent is used for both topical and systemic administration.

Conclusions

Antimicrobial agents should be used prudently while promoting antimicrobial stewardship in each institution, local area, and country. The recent global spread of antimicrobial resistance gives us warning in current practice. TG13 provides a practical guide for physicians and surgeons who are involved in the management of community-acquired and healthcare-associated acute biliary infections. There are still many areas of uncertainty in this subject. Continuous monitoring of local antimicrobial resistance and further studies on acute cholangitis and cholecystitis should be warranted.

Conflict of interest None.

References

TG13 indications and techniques for biliary drainage in acute cholangitis (with videos)

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Abstract The Tokyo Guidelines of 2007 (TG07) described the techniques and recommendations of biliary decompression in patients with acute cholangitis. TG07 recommended that endoscopic transpapillary biliary drainage should be selected as a first-choice therapy for acute cholangitis because it is associated with a low mortality rate and shorter duration of hospitalization. However, TG07 did not include the whole technique of standard endoscopic transpapillary biliary drainage, for example, biliary cannulation techniques including contrast medium-assisted cannulation, wire-guided cannulation, and treatment of duodenal major papilla using endoscopic papillary balloon dilation (EPBD). Furthermore, recently single-or double-balloon enteroscopy-assisted biliary drainage (BE-BD) and endoscopic ultrasonography-guided biliary drainage (EUS-BD) have been reported as special techniques for biliary drainage. Nevertheless, the updated Tokyo Guidelines (TG13) recommends that endoscopic drainage should be first-choice treatment for biliary decompression in patients with non-surgically altered anatomy and suggests that the choice of cannulation technique or drainage method (endoscopic naso-biliary drainage and stenting) depends on the endoscopist’s preference but EST should be selected rather than EPBD from the
aspect of procedure-related complications. In terms of BE-BD and EUS-BD, although there are many reports on their usefulness, they should be performed by skilled endoscopists in high-volume institutes, who are good at enteroscopy or echoendosonography, respectively, because procedures and devices are not yet established.


Keywords  Cholangitis · Percutaneous biliary drainage · Endoscopic biliary drainage · Endoscopic cholangiopancreatography · Guidelines

Introduction

Acute cholangitis varies in severity, ranging from a mild form which can be treated by conservative therapy to a severe form which leads to a life-threatening state, e.g. shock state and altered sensorium. In particular, the severe form often results in mortality in the elderly [1–3]. Biliary drainage, which is the most essential therapy for acute cholangitis, is divided into three types, surgical, percutaneous transhepatic, and endoscopic drainage. Of these therapies, it is well known that surgical intervention leads to the highest mortality rate [1]. Recently, mortality due to acute cholangitis has decreased due to development of percutaneous transhepatic cholangial drainage (PTCD) [4] and endoscopic biliary drainage [5, 6]. Nevertheless, acute cholangitis can still be fatal unless it is treated in a timely way. The Tokyo Guidelines of 2007 (TG07) described the fundamental biliary drainage techniques for acute cholangitis [7]. Subsequently, new biliary drainage techniques for the therapy of acute cholangitis have been reported. Herein, we describe the indications and techniques of biliary drainage for acute cholangitis in the updated Tokyo Guidelines (TG13).

Indications and techniques of biliary drainage

In TG13, biliary drainage is recommended for acute cholangitis regardless of degree of severity other than some cases of mild acute cholangitis in which antibiotics and general supportive care are effective.

Q1. What is the most preferable biliary drainage? endoscopic vs percutaneous vs surgical drainage for acute cholangitis?

We recommend endoscopic biliary drainage for acute cholangitis (recommendation 1, level B).

We suggest that percutaneous transhepatic biliary drainage may be considered as alternative methods when endoscopic biliary drainage is difficult (recommendation 2, level C).

Endoscopic drainage should be considered the first-choice drainage procedure because several studies have described it as less invasive than other drainage techniques [7–11].

Percutaneous transhepatic cholangial drainage (supplement video 1)

Indications

Nowadays, percutaneous transhepatic cholangial drainage (PTCD), also known as percutaneous transhepatic biliary drainage (PTBD), has become the second choice of therapy for acute cholangitis following endoscopic drainage because of possible complications, including intraperitoneal hemorrhage and biliary peritonitis, and the need for a long hospital stay. However, PTCD can still be conducted in any of the following circumstances: (1) in patients with an inaccessible papilla due to upper GI tract obstruction, as in duodenal obstruction or surgically altered anatomy like Whipple resection or Roux-en-Y anastomosis, in which the passage of endoscope or endoscopic drainage is thought to be difficult or impossible; (2) when skilled pancreaticobiliary endoscopists are not available in the institution. Furthermore, even in patients with non-surgically altered anatomy, PTCD can be salvage therapy when conventional endoscopic drainage has failed. In general, coagulopathy is a relative contraindication. However, if there is no other life-saving method, PTCD would be indicated.

Techniques

Before the prevalence of transabdominal ultrasonography, needle puncture of the bile duct was conducted under fluoroscopy [4]. Currently, needle puncture is safely performed under ultrasonography to avoid the intervening blood vessel [12]. Therefore, in the current PTCD procedure, operators should continuously observe the bile duct using ultrasonography regardless of the presence of
The PTCD procedure is performed as follows, and as previously described [4]. Briefly, at first, ultrasonography-guided transhepatic puncture of the intrahepatic bile duct is conducted using an 18- to 22-G needle. After confirming backflow of bile, a guidewire is advanced into the bile duct. Finally, a 7- to 10-Fr catheter is placed in the bile duct under fluoroscopic control over the guidewire. Puncture using a small-gauge (22-G) needle is safer in patients without biliary dilation than with biliary dilation. According to the Quality Improvement Guidelines produced by American radiologists, the success rates of drainage are 86 % in patients with biliary dilation and 63 % in those without biliary dilation [12].

**Surgical drainage**

**Indications**

In benign diseases like bile duct stones, surgical drainage is extremely rare because of the prevalence of endoscopic drainage or PTCD for the therapy of acute cholangitis. However, in patients with acute cholangitis due to unresectable neoplasms like cancer of the pancreatic head, hepaticojejunostomy can be performed as bypass surgery only in limited patients without severe acute cholangitis. In particular, when periampullary neoplastic lesions like cancer of the pancreatic head or ampullary cancer, show both acute cholangitis and duodenal obstruction, double bypass surgery, hepaticojejunostomy and gastrojejunostomy, may be a rare choice.

**Techniques**

Open drainage for decompression of the bile duct is performed as a surgical intervention. When surgical drainage in critically ill patients with bile duct stones is performed, prolonged operations should be avoided and simple procedures, such as T-tube placement without choledocholithotomy, are recommended [13].

**Endoscopic biliary drainage**

**Indications**

Endoscopic transpapillary biliary drainage has become the gold standard technique for acute cholangitis, regardless of whether the pathology is benign or malignant, because it is a minimally invasive drainage method [4]. On the other hand, endoscopic drainage using a standard duodenoscope in patients with duodenal obstruction and surgically altered anatomy, like Roux-en-Y anastomosis, seems to be contraindicated.

The timing of endoscopic biliary drainage is very important for the clinical outcome. Khashab et al. [14] described that delayed (more than 72 h after administration) and unsuccessful ERCP are associated with worse outcomes in patients with acute cholangitis. Actually, in TG07, two thirds of outstanding pancreatobiliary surgeons and endoscopists supported the use of emergent or early drainage in patients with moderate or severe cholangitis [15].

**Techniques**

**Biliary cannulation**

Biliary cannulation should be conducted in advance of biliary drainage. Basically, there are two biliary cannulation techniques, namely contrast medium-guided cannulation (standard cannulation) and wire-guided cannulation.

**Q2. What technique should be used for biliary cannulation? Standard cannulation or wire-guided cannulation?**

We suggest that either standard cannulation or wire-guided cannulation can be considered for bile duct access (recommendation 2, level B).

Two meta-analyses of a randomized controlled trial (RCT) on the comparison between standard cannulation and wire-guided cannulation showed that wire-guided cannulation was able to increase the successful biliary cannulation rate and prevent post-ERCP pancreatitis [16, 17]. Recently, however, two RCTs have shown that there is no statistically significant difference between standard cannulation and wire-guided cannulation on the success rate of biliary cannulation or the prevention rate of post-ERCP pancreatitis [18, 19]. Therefore, the choice of techniques for biliary cannulation is still controversial.

When biliary cannulation using standard cannulation or wire-guided cannulation techniques fails, precutting, which means an incision of the papilla enabling the bile duct orifice to be opened for biliary cannulation, may be performed if an alternative method, like PTCD or surgical intervention, is not performed. In the main, two types of precutting methods are used. Needle knife precutting using needle-type sphincterotome is well known as a basic precutting method (Fig. 1a). Alternatively, several endoscopists prefer pancreatic sphincter precutting using a pull-type sphincterotome for biliary access (Fig. 1b). The use of precutting methods depends on the institution and endoscopist. It is known that precutting is likely to cause serious complications, such as acute pancreatitis and perforation, and therefore it should be performed only by skilled endoscopists [20, 21].
Endoscopic naso-biliary drainage and endoscopic biliary stenting

Indications

Endoscopic transpapillary biliary drainage is divided into two types: endoscopic naso-biliary drainage (ENBD) as an external drainage and endoscopic biliary stenting (EBS) as an internal drainage. Although, basically, both endoscopic biliary drainage types can be conducted in all acute cholangitis, they may be contraindicated in patients in whom the endoscope cannot reach the papilla due to GI tract obstruction or surgically altered anatomy, or in whom endoscopic procedures are inadequate because of critical illness. In particular, ENBD should be avoided in patients with poor compliance, who may remove the tube, and those with abnormalities of the nasal cavity causing difficulty in naso-biliary tube insertion.

In the case of biliary drainage for therapy of acute cholangitis, skilled endoscopic technique is mandatory because long and unsuccessful procedures may lead to serious complications in critical ill patients. Therefore, endoscopists who perform endoscopic biliary drainage in these patients, should already have a high success rate of biliary cannulation including the precutting technique.

Q3. What procedure should be used for endoscopic biliary drainage? ENBD or EBS?

We suggest that either ENBD or EBS may be considered for biliary drainage (recommendation 2, level B).

Three comparative studies have shown that there is no statistically significant difference in technical success, clinical success, complications and mortality between ENBD and EBS, although a visual analogue scale was higher in the ENBD group than in the EBS group (Table 1) [22–24]. In consequence of these results, TG13 suggests that either drainage procedure can be selected according to the preference of the endoscopist. However, if ENBD is selected for the treatment of acute cholangitis, we should bear in mind that if the patient has discomfort from the transnasal tube placement, they are likely to remove the tube themselves, especially elderly patients.

One RCT has revealed that biliary drainage is not mandatory after endoscopic clearance of the common bile duct in patients with choledocholithiasis-induced cholangitis (level B) [25].

Techniques

**ENBD (supplement video 2)**

ENBD procedures are described in detail in TG07 [4]. Briefly, after selective biliary cannulation, a 5-Fr to 7-Fr tube is placed in the bile duct as an external drainage over the guidewire (Fig. 2a).

**EBS (supplement video 3)**

EBS procedures is also described in the previous guideline [4]. In brief, after selective biliary cannulation, a 7-
10-Fr plastic stent is placed in the bile duct as an internal drainage over the guidewire. There are two different stent shapes, a straight type with a single flap with a sidehole (Amsterdam type) (Fig. 2b) or radial flaps without a side-hole (Tannenbaum type) on both sides, and a double pig-tail type to prevent inward and outward stent migration. There is no comparative study between straight type and pig-tail type stents. Therefore, either stent can be selected according to the preference of the endoscopist.

### Treatment of the major papilla

#### Endoscopic sphincterotomy (EST)

**Indications**

EST technique is usually used for stone removal and, at times, prevention of the occlusion of the pancreatic duct orifice by placement of a large-bore biliary stent (more than 10-Fr or a self-expandable metal stent).

**Q4. Is EST necessary in endoscopic biliary drainage?**

We suggest that addition of EST should be determined according to the patient’s condition and the operator’s skill (recommendation 2, level C).

We suggest that EST followed by stone removal without biliary drainage can be recommended as an alternative procedure in patients with choledocholithiasis-induced acute cholangitis (recommendation 2, level C).

As TG07 described, an additional EST is not necessary in acute cholangitis as follows: (1) additional EST causes complications such as hemorrhage [26, 27]; (2) post-EST hemorrhage is one of the risk factors of acute cholangitis [20]. In particular, the use of EST in patients with severe (grade III) disease complicated by coagulopathy should be avoided. Nevertheless, EST has some advantages as follows: (1) it provides not only drainage but also clearance of bile duct stones at a single session in patients with choledocholithiasis (not complicated by severe cholangitis). (2) Precutting can allow bile duct access, providing biliary drainage in patients in whom selective biliary cannulation is impossible using the standard cannulation technique. In particular, stone removal in one session can shorten the hospital stay. Therefore, TG13 suggests that addition of EST should be determined according to the patient’s condition and the operator’s skill.

### Techniques

The detail of EST procedures is described in TG07 [4]. Briefly, after selective biliary cannulation with or without a guidewire, a pull-type sphincterotomy incision is performed below the transverse fold (Fig. 3). When the transverse fold is not present, the superior margin of the papilla bulge is used as a landmark to determine the length of the sphincterotomy (supplement video 4). An electrosurgical generator with a controlled cutting system (Endocut mode, ICC200, VIO300, ERBE Elektromedizin GmbH, Tubingen, Germany) is used for EST; the push-type is used for EST in patients with Billroth II gastrectomy or Roux-en-Y anastomosis. Only a limited incision is necessary in EST for drainage purposes using a large-bore stent, unlike that for stone removal [10]. Endoscopists should remember that EST may cause acute pancreatitis or cholangitis, which may become life-threatening when severe [20].
Endoscopic papillary balloon dilation (EPBD)

Indications

The EPBD procedure is usually used instead of EST for removal of bile duct stones [28]. Until now, there has been no comparative study on the use of EPBD during biliary drainage to treat acute cholangitis due to bile duct stones. EPBD, like EST, has the advantage of reducing the number of therapeutic sessions and shortening the hospital stay in patients with acute cholangitis caused by bile duct stones. One systematic review revealed that EPBD is statistically less successful for stone removal, requires higher rates of mechanical lithotripsy, and carries a higher risk of pancreatitis, although it also has statistically significant lower rates of bleeding [29]. Thus, TG13 suggests that EPBD appears to be useful for treatment in patients who have coagulopathy and acute cholangitis caused by a small stone.

On the other hand, theoretically, since the aim of EPBD is to preserve the function of the sphincter of Oddi, EPBD alone without biliary drainage is contraindicated for the therapy of acute cholangitis. In addition, EPBD should be avoided in patients with biliary pancreatitis.

Techniques

After selective biliary cannulation, a small balloon up to 8-mm in diameter, depending on the diameters of the bile duct and the stone, is advanced into the bile duct across the papilla. Then, the sphincter of Oddi is gradually dilated by inflation of the balloon until the waist of the balloon disappears. Then, clearance of the bile duct stone is conducted using a basket catheter and balloon catheter.

Special techniques of endoscopic biliary drainage

Recently, several new techniques of endoscopic biliary drainage have been developed.
Balloon enteroscope-assisted bile duct drainage

Indications

ERCP in patients with surgically altered anatomy can be challenging. In general, Roux-en-Y anastomosis has been thought to preclude endoscopic access for ERCP because of the extensive lengths of the efferent and afferent limbs that must be traversed to reach the major papilla or hepaticojejunostomy site. Recently, single balloon enteroscopy (SBE) and double balloon enteroscopy (DBE) have enabled successful ERCP to be performed in patients with such surgically altered anatomy. Several investigators have reported various success rates (40 to 95 %) with adverse events rates below 5 % (Tables 2, 3) [30–42]. However, since this technique may be unsuccessful and time-consuming, its indication should be cautiously decided. Although ideal operators are those who are skilled in both balloon enteroscopy and ERCP, in some institutions, GI endoscopists advance an endoscope to the papilla or anastomotic site and then pancreaticobiliary endoscopists perform ERCP. Therefore, if the operators are not good at this technique, therapy using balloon enteroscopy should be avoided.

Techniques (supplement video 5)

The SBE and DBE balloon system consists of a video enteroscope (XSIF-Q260Y; Olympus Medical Systems, Tokyo, Japan and long-type DBE: EN-450T5, short-type DBE: EC-450B15/EI-530B, Fujifilm Co., Ltd., Saitama, Japan), a sliding tube with a balloon and a balloon controller. The DBE has a balloon at the tip of the endoscope in addition to the balloon of the overtube. Endoscopes are advanced to the papilla or anastomotic site using the pushing and pulling techniques (Fig. 4a, b). An injection catheter and a tapered catheter are used for initial cannulation. First, 0.025–0.035-inch guidewires are inserted into the bile duct. Finally, 5–8.5-Fr naso-biliary drainage catheters and self-expandable metallic stents are placed into the bile duct for biliary decompression. In cases requiring an endoscopic sphincterotomy, a sphincterotome and needle knife are advanced into the bile duct over or alongside the guidewire. In cases of EPBD, a conventional dilation catheter is used for the papilla or

Table 2 Outcome of single-balloon enteroscopy-assisted ERCP

<table>
<thead>
<tr>
<th>References</th>
<th>n</th>
<th>Technical success (1st attempt) (%)</th>
<th>Adverse events (%)</th>
</tr>
</thead>
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<td>Itoi [30]</td>
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<td>72</td>
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<tr>
<td>Saleem [31]</td>
<td>56</td>
<td>91</td>
<td>None</td>
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<tr>
<td>Wang [32]</td>
<td>12</td>
<td>90</td>
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<tr>
<td>Total</td>
<td>79</td>
<td>89</td>
<td>2.50</td>
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Table 3 Outcome of double-balloon enteroscopy-assisted ERCP (n ≥ 5)

<table>
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<th>Adverse events (%)</th>
</tr>
</thead>
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<td>40</td>
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<td>Emmett [35]</td>
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<td>Aabakken [36]</td>
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<td>Kuga [38]</td>
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<td>Shimatani [40]</td>
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<td>Tsujino [41]</td>
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<tr>
<td>Itoi [42]</td>
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<tr>
<td>Total</td>
<td>151</td>
<td>86</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Fig. 4 Balloon enteroscope-assisted ERCP. a ERCP in esophagojejunostomy with Roux-en-Y patient. b ERCP in hepaticojejunostomy with Roux-en-Y patient.
hepaticojejunostomy site. When selective cannulation is not possible, a needle knife is used for pre-cutting. A basket catheter, retrieval balloon catheter, and/or mechanical lithotripter are used for removal of stones.

Endoscopic ultrasonography-guided bile duct drainage

Indications

Recently, endoscopic ultrasonography (EUS)-guided biliary drainage has been reported as a salvage therapy when standard endoscopic drainage has failed [43–54]. Since the technique and devices of this procedure are not yet established and there is no dedicated device for this procedure, it should be conducted only in selected patients in whom standard biliary drainage by means of ERCP or PTCD has failed or is contraindicated for various reasons like considerable ascites. There are two methods of approach in EUS-guided biliary drainage: (1) EUS-guided intrahepatic bile duct drainage (Fig. 5a) by a transesophageal, transgastric or transjejunal approach; (2) EUS-guided extrahepatic bile duct drainage (Fig. 5b) by a transduodenal or transgastric approach. The choice of drainage route depends on the presence of a gastric outlet obstruction and the stricture site of the bile duct. Several published data on EUS-guided intrahepatic bile duct drainage and extrahepatic bile duct drainage show that the success rate is high (95%), with 93–100 % (intention-to-treat) response rates (Table 4) [43–54]. Most of the reported cases of adverse events were pneumoperitonitis but there was no serious adverse event. However, since the procedure is not yet established, it should be conducted by endoscopists skilled in both echoendosonography and ERCP.

Techniques [55] (supplement video 6 and video 7)

Theoretically, the intrahepatic bile duct and liver, including the extrahepatic bile duct does not adhere to the GI tract. Therefore, there is a possibility of bile leakage during the procedure; particularly, if the procedure fails, serious bile peritonitis can occur. A needle knife (Zimmon papillotomy knife, or Cystotome, Wilson-Cook, Winston-Salem, NC) catheter using electrocautery (EndoCut ICC200, VIO300D, ERBE Elektromedizin GmbH, Tübingen, Germany), or a 19-gauge needle (EchoTip, Wilson-Cook), is advanced into the bile duct under EUS visualization after confirming the absence of intervening blood vessels to avoid bleeding. After the stylet is removed, bile is aspirated and then contrast medium is injected into the gallbladder for cholecystography, then a 450 cm long, 0.025- or 0.035-inch guidewire is advanced into the outer sheath. If necessary, a biliary catheter for dilation (Soehendra Biliary Dilator, Wilson-Cook), papillary balloon dilation catheter (Maxpass, Olympus Medical Systems), and electrical cautery needle, are used for dilation of the hepaticoenterostomy site and choledochoenterostomy site. Finally, a 7-Fr plastic stent or a self-expandable metal stent are advanced into the bile duct.
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Conflict of interest None.

References


TG13 indications and techniques for gallbladder drainage in acute cholecystitis (with videos)

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Abstract Percutaneous transhepatic gallbladder drainage (PTGBD) is considered a safe alternative to early cholecystectomy, especially in surgically high-risk patients with acute cholecystitis. Although randomized prospective controlled trials are lacking, data from most retrospective studies demonstrate that PTGBD is the most common gallbladder drainage method. There are several alternatives to PTGBD. Percutaneous transhepatic gallbladder aspiration is a simple alternative drainage method with fewer complications; however, its clinical usefulness has been shown only by case-series studies. Endoscopic naso-gallbladder drainage and gallbladder stenting via a transpapillary endoscopic approach are also alternative methods in acute cholecystitis, but both of them have technical difficulties resulting in lower success rates than that of PTGBD. Recently, endoscopic ultrasonography-guided transmural gallbladder drainage has been reported as a special technique for gallbladder drainage. However, it is not yet an established technique. Therefore, it should be performed in high-volume institutes by skilled endoscopists. Further prospective evaluations of the feasibility, safety, and efficacy of these various approaches are needed. This article

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describes indications and techniques of drainage for acute cholecystitis.


Keywords Acute cholecystitis · Gallbladder drainage · Endoscopic ultrasound · Percutaneous transhepatic gallbladder drainage (PTGBD) · Endoscopic naso-gallbladder drainage (ENGBD)

Introduction

The Tokyo Guidelines (TG07) defined diagnostic criteria and severity assessment of acute cholecystitis in January 2007[1]. In the TG07, percutaneous transhepatic gallbladder drainage (PTGBD) should be used in patients with grade II (moderate) cholecystitis only when they do not respond to conservative treatment and for patients with grade III (severe) disease [2]. One controlled study (level C) [3] compared PTGBD with medical treatment alone and did not find lower mortality using PTGBD, but this study has several serious limitations as follows; (1) selection bias [the PTGBD group had many intensive care unit (ICU) patients], (2) drainage methods were changed after a fatal complication, (3) randomization was achieved using a playing card and was not blinded. Thus, PTGBD, which has been endorsed by many studies of case-series but not by proper controlled trials (level C) [4–14], is the most common gallbladder drainage method for elderly and critically ill patients. There are several alternatives to PTGBD. Percutaneous transhepatic gallbladder aspiration (PTGBA) is an alternative in which the gallbladder contents are puncture-aspirated without placing a drainage catheter (level C) [6, 15]. Endoscopic naso-biliary gall-bladder drainage (ENGBD) and endoscopic gallbladder stenting (EGBS) are also alternatives via the transpapillary route [16]. With the recent improvement in endoscopic ultrasound (EUS), EUS-guided gallbladder drainage is performed via the antrum of the stomach and the bulb of the duodenum [16]. However, these alternatives are not fully examined; PTGBD is still recognized as a standard drainage method.

In this article, we describe the indication and details of gallbladder drainage for acute cholecystitis, and show the grades of recommendation for the procedures established by the Guidelines.

Q1. What are the standard gallbladder drainage methods for surgically unfit patients with acute cholecystitis?

We recommend PTGBD as a standard drainage method according to the GRADE system [17]. Factors that affect the strength of a recommendation are summarized in Table 1.

Indications and significance of PTGBD

Although early cholecystectomy, a one-shot definitive treatment for acute cholecystitis, remains the reference standard, perioperative mortality rates in elderly or critically ill patients are reported to be high (up to 19 %) [18]. Therefore, PTGBD is considered a safe alternative, especially in surgically high-risk populations. There is no doubt that PTGBD with administration of antibiotics can convert a septic cholecystitis into a non-specific condition. From a technical point of view, it is a rather uncomplicated procedure with a low complication rate reported to range from 0 to 13 % [4–12]. A systematic review [18] reports that 30-day or in-hospital mortality after PTGBD is high (15.4 %), but that procedure-related mortality is low (0.36 %). Of note, mortality is predominantly related to the severity of the underlying disease rather than the ongoing gallbladder sepsis. By contrast, mortality rates after cholecystectomy in elderly patients with acute cholecystitis have been lower than those of previous years (prior to 1995 vs. after 1995, 12.0 vs. 4.0 %) [18]. Recent advances in anesthesiology and perioperative care may have improved the outcomes of cholecystectomy for critically ill patients. There are no controlled studies evaluating the outcomes of...
PTGBD versus early cholecystectomy. A few papers report comparative studies in a well-defined patient group. Melloul et al. [19] analyzed a matched case-controlled study of critically ill patients with acute cholecystitis. A series of 42 consecutive patients at a single ICU center during a 7-year period were retrospectively analyzed. Surgery was associated with an increased complication rate of 47% compared with PTGBD (8.7%), but mortality rates were not different. One Spanish retrospective study [20] compared mortality rates in 62 consecutive patients critically ill with acute cholecystitis divided between a PTGBD group and a cholecystectomy group, and they found a significantly higher mortality rate in the PTGBD group (17.2 vs. 0%). This study, however, has several limitations: the study design is not prospective, inclusion criteria in the PTGBD group may have selection bias because the highest-risk patients could have been treated mainly by PTGBD. These biases and shortcomings in the study design make any comparison between the outcomes of PTGBD and early cholecystectomy hazardous. Therefore, it is not possible to make definitive recommendations regarding treatment using PTGBD or cholecystectomy in elderly or critically ill patients with acute cholecystitis. Large multicenter randomized trials of PTGBD versus early cholecystectomy are undoubtedly needed to resolve these controversies.

**Optimal timing of gallbladder drainage**

For patients with moderate (grade II) disease, gallbladder drainage should be used only when a patient does not respond to conservative treatment. For patients with severe (grade III) disease, gallbladder drainage is recommended with intensive care. One prospective study [21] shows that predictors for failure of conservative treatment are: age above 70 years old, diabetes, tachycardia and a distended gallbladder at admission. Likewise, WBC >15000 cell/μl, an elevated temperature and age above 70 years old were found to be predictors for the failure of conservative treatment at 24-h and 48-h follow-up.

**Procedures for gallbladder drainage**

**Percutaneous transhepatic gallbladder drainage (Video 1)**

PTGBD is a standard technique for nonoperative gallbladder drainage. After ultrasound-guided transhepatic gallbladder puncture has been performed with an 18-G needle, a 6- to 10-Fr pigtail catheter is placed in the gallbladder, using a guidewire under fluoroscopy (Seldinger technique; Fig. 1). There was no technical difficulty and the technique could be available around the world (Table 1). However, it has several disadvantages as follows: (1) the drainage tube cannot be extracted until a fistula forms around the tube, (2) there is a risk of dislocation of the tube, (3) patient discomfort may cause self-decannulation of the PTGBD tube.

**Percutaneous transhepatic gallbladder aspiration**

PTGBA is a method to aspirate bile via the gallbladder with a small-gauge needle under ultrasonographic guidance (Fig. 2). This method is an easy low-cost bedside-applicable procedure, without the patient discomfort seen in PTGBD (Table 1). Theoretically, the drainage effect of single PTGBA is lower than that of PTGBD as described in a randomized controlled trial (RCT) [12]. However, repetitive PTGBA [6, 15] can improve its effectiveness (from 71.1 to 95.6%) and this methodology has not been compared with PTGBD. Although PTGBA with a small-gauge (21-G) needle has a lower risk of leakage after removal, aspiration of highly viscous bile is difficult with such needles and should be conducted while washing with saline containing antibiotics.

**Endoscopic transpapillary gallbladder drainage**

Endoscopic naso-biliary gallbladder drainage (Video 2)

ENGBD can be used for patients with severe comorbid conditions, especially those with end-stage liver disease, in

---

**Table 1** A critical comparison of drainage methods for acute cholecystitis according to GRADE system [17]

<table>
<thead>
<tr>
<th>Drainage method</th>
<th>Quality of evidence</th>
<th>The balance between desirable and undesirable effects</th>
<th>Technical difficulty</th>
<th>Patient values and preferences</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTGBD</td>
<td>B (moderate)</td>
<td>Very good</td>
<td>No</td>
<td>Yes</td>
<td>Low cost</td>
</tr>
<tr>
<td>PTGBA</td>
<td>C (low)</td>
<td>Good (insufficient drainage effect)</td>
<td>No</td>
<td>No</td>
<td>Very low cost</td>
</tr>
<tr>
<td>ENGBD/EGBS</td>
<td>C (low)</td>
<td>Good (low success rate)</td>
<td>Yes (difficult)</td>
<td>Yes/no</td>
<td>Low cost</td>
</tr>
<tr>
<td>Surgical cholecystostomy</td>
<td>C (low)</td>
<td>Good (surgical risk)</td>
<td>No</td>
<td>Yes</td>
<td>High cost</td>
</tr>
</tbody>
</table>

*See details in each section*
Fig. 1  Percutaneous transhepatic gallbladder drainage (PTGBD) procedure. A guidewire is inserted into the gallbladder after a needle is inserted into the gallbladder (left). Then a drainage tube is passed over the guide-wire into the gallbladder (right).

Fig. 2  Percutaneous transhepatic gallbladder aspiration (PTGBA) procedure. Under ultrasound guidance, the gallbladder is punctured transhepatically by a needle (left). Then bile is aspirated by using a syringe (right).

Fig. 3  Endoscopic nasobiliary gallbladder drainage (ENGBD) procedure. Left: Schema of ENGBD. Right: X-ray shows nasobiliary catheter placed in the gallbladder.
whom the percutaneous approach is difficult to perform. However, because it requires a difficult endoscopic technique (technical success rate varies from 64 to 100%), and relevant case-series studies have been conducted only at a limited number of institutions [22–28], ENGBD has not yet been established as a standard method. Therefore, it should be performed in high-volume institutes by skilled endoscopists.

ENGBD involves placement of a naso-gallbladder drainage tube and generally does not require biliary sphincterotomy. After successful bile duct cannulation, a 0.035-in. guidewire is advanced into the cystic duct and subsequently into the gallbladder. At times, a hydrophilic guidewire is useful for seeking the cystic duct. Finally, a 5–8.5 Fr pigtail naso-gallbladder drainage tube catheter is placed into the gallbladder (Fig. 3).

Endoscopic transpapillary gallbladder stenting

Since endoscopic transpapillary gallbladder stenting (EGBS) requires a difficult endoscopic technique, and relevant case-series studies have been conducted only at a limited number of institutions [29–36], EGBS also has not been established as a standard method. Therefore, it should be performed in high-volume institutes by skilled endoscopists. The procedure is identical to ENGBD, but a 6–10-Fr diameter double pigtail stent is placed (Fig. 4). When 10-Fr stents or a gallbladder stent and a biliary stent are placed (for example in Mirizzi’s syndrome), an endoscopic biliary sphincterotomy is performed to prevent post-ERCP pancreatitis.

Q2. What are the special techniques as gallbladder drainage?

EGBS procedure.

**There is endoscopic ultrasonography-guided gallbladder drainage (EUS-guided gallbladder drainage).**

EUS-guided gallbladder drainage is performed via the antrum of the stomach and bulbus of the duodenum (Fig. 5) [16, 42]. It includes EUS-guided naso-gallbladder drainage [37, 38] and EUS-guided gallbladder stenting [39, 44] (Table 2). Recently one controlled study [42] showed that EUS-GBD is comparable to PTGBD in terms of the technical feasibility and efficacy. However, EUS-guided gallbladder drainage has not been established as a standard method. Therefore, they should be performed in high-volume institutes by skilled endoscopists [37–46].

**Technique of EUS-guided gallbladder drainage [16, 44] (Video 3)**

Theoretically, the gallbladder does not have adhesions to the GI tract. Therefore, there is a possibility of bile leakage
during the procedures; in particular, if the procedure fails, serious bile peritonitis can occur. The choice of endoscope position is important to accomplish the procedure safely. The gallbladder is visualized from the duodenal bulb or the antrum of the stomach using a curved linear array echoendoscope in a long scope position (pushing scope position) (Fig. 5). At this time, the direction of the EUS probe is toward the right side of the body. A needle knife (Zimmon papillotomy knife, or Cystotome, Wilson-Cook, Winston-Salem, NC, USA) catheter using electrocautery, or a 19-gauge needle (EchoTip, Wilson-Cook), is advanced into the gallbladder under EUS visualization after confirming the absence of intervening blood vessels to avoid bleeding. After the stylet has been removed, first bile is aspirated and then contrast medium is injected into the gallbladder for cholecystography, then a 0.025- or 0.035-in. guidewire is advanced into the outer sheath. If necessary, a biliary catheter for dilation (Soehendra Biliary Dilator, Wilson-Cook), or papillary balloon dilation catheter (Maxpass, Olympus Medical Systems) are used for dilation of the gastrocholecystic and duodenocholecystic fistula. Finally, a 5-10 Fr naso-gallbladder tube is advanced via the cholecystogastrostomy and choledochojejunostomy site into the gallbladder. The basic procedure of EUS-guided gallbladder stenting is the same as EUS-guided naso-gallbladder drainage. A 7-10Fr double pigtail plastic or self-expanding metallic stent is placed in the final step.

Table 2  Outcome of endosonography-guided gallbladder drainage

<table>
<thead>
<tr>
<th>References</th>
<th>No. of cases</th>
<th>NGD/Stenting</th>
<th>Approach route</th>
<th>Technical success (%)</th>
<th>Clinical success (%)</th>
<th>Complication (no. of cases)</th>
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<td>Baron [39]</td>
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<td>TD</td>
<td>100</td>
<td>100</td>
<td>None</td>
<td></td>
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<td>Kwan [37]</td>
<td>3 NGD</td>
<td>TD</td>
<td>100</td>
<td>100</td>
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<td>Lee [38]</td>
<td>9 NGD</td>
<td>TD</td>
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<tr>
<td>Takasawa [40]</td>
<td>1 PS</td>
<td>TG</td>
<td>100</td>
<td>100</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Kamata [46]</td>
<td>1 SEMS</td>
<td>TD</td>
<td>100</td>
<td>100</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Song [41]</td>
<td>8 PS</td>
<td>1TG/7TD</td>
<td>100</td>
<td>100</td>
<td>Bile leakage (1) a, pneumoperitoneum (1), stent migration (1)</td>
<td></td>
</tr>
<tr>
<td>Itoi [42]</td>
<td>2 PS</td>
<td>1TG/1TD</td>
<td>100</td>
<td>100</td>
<td>Bile leakage (1) a</td>
<td></td>
</tr>
<tr>
<td>Jang [43]</td>
<td>15 SEMS</td>
<td>10TG/5TD</td>
<td>100</td>
<td>100</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Itoi [44]</td>
<td>5 SEMS</td>
<td>1TG/4TD</td>
<td>100</td>
<td>100</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Jang [45]</td>
<td>30 NGD</td>
<td>NA</td>
<td>97</td>
<td>100</td>
<td>Pneumoperitoneum (2)</td>
<td></td>
</tr>
</tbody>
</table>

SEMS self-expandable metal stent, PS plastic stent, NGD naso-gallbladder drain, TD transduodenal approach, TG transgastric approach, NA not available

a Minor bile leakage without serious bile peritonitis

Fig. 5  EUS-guided gallbladder approach via bulbus of the duodenum. Left Schema of EUS-guided gallbladder drainage. Right X-ray shows double-pig tail stent placed in the gallbladder.
100%, but the incidence of accidents was fairly high (11–33%), indicating the necessity for further investigations emphasizing safety evaluation. There are several possible procedure-related early adverse events, e.g., bile leakage, stent migration into the gallbladder or intra-abdominal space, deviation of stent from the gallbladder, puncture-induced hemorrhage, and perforation of peritoneum. Late adverse events include relapse of acute cholecystitis due to stent occlusion, and inadvertent tube removal.

**Conflict of interest** None.

**References**


LG13 surgical management of acute cholecystitis

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Abstract

Background Laparoscopic cholecystectomy is now accepted as a surgical procedure for acute cholecystitis when it is performed by an expert surgeon. There are several lines of strong evidence, such as randomized controlled trials (RCTs) and meta-analyses, supporting the introduction of laparoscopic cholecystectomy for patients with acute cholecystitis. The updated Tokyo Guidelines 2013 (TG13) describe the surgical treatment for acute cholecystitis according to the grade of severity, the timing, and the procedure used for cholecystitis in a question-and-answer format using the evidence concerning surgical management of acute cholecystitis.

Methods and materials Forty-eight publications were selected for a careful examination of their full texts, and the types of surgical management of acute cholecystitis were investigated using this evidence. The items concerning the surgical management of acute cholecystitis were the optimal surgical treatment for acute cholecystitis according to...
the grade of severity, optimal timing for the cholecystectomy, surgical procedure used for cholecystectomy, optimal timing of the conversion of cholecystectomy from laparoscopic to open surgery, and the complications of laparoscopic cholecystectomy.

**Results** There were eight RCTs and four meta-analyses concerning the optimal timing of the cholecystectomy. Consequently, it was found that cholecystectomy is preferable early after admission. There were three RCTs and two meta-analyses concerning the surgical procedure, which concluded that laparoscopic cholecystectomy is preferable to open procedures. Literature concerning the surgical treatment according to the grade of severity could not be quoted, because there have been no publications on this topic. Therefore, the treatment was determined based on the general opinions of professionals.

**Conclusion** Surgical management of acute cholecystitis in the updated TG13 is fundamentally the same as in the Tokyo Guidelines 2007 (TG07), and the concept of a critical view of safety and the existence of extreme vasculobiliary injury are added in the text to call the surgeon’s attention to the need to reduce the incidence of bile duct injury.


**Keywords** Acute cholecystitis · Laparoscopic cholecystectomy · Cholecystostomy · Bile duct injury · Gallbladder drainage

**Introduction**

Cholecystectomy has been widely used as a surgical procedure for acute cholecystitis. There have been several studies on the timing of cholecystectomy beginning in the era of open surgery and also in the current era of laparoscopic surgery. These studies have shown that early surgery conducted within 72–96 h after the onset of symptoms is associated with advantages such as reduced hospital stay, sick leave, and health care expenditures, and no disadvantages with regard to mortality and morbidity. Since the initial introduction of laparoscopic cholecystectomy, it has been considered to be contraindicated for acute cholecystitis. However, due to the establishment of the critical view of safety introduced by Strasberg et al. [1] for the dissection of Calot’s triangle, the development of new techniques, and the improvements made to the instruments used for endoscopic surgery, laparoscopic cholecystectomy is now accepted as a safe surgical technique when it is performed by expert surgeons. Recent randomized clinical trials and meta-analyses have indicated that laparoscopic cholecystectomy is preferable to open cholecystectomy.

In 2007, the Tokyo Guidelines for the management of acute cholangitis and cholecystitis [2] were published in the Journal of Hepato-Biliary-Pancreatic Surgery, in which a severity classification was presented for the first time. Previously, there was no severity classification for acute cholecystitis. There were therefore no reports of the effects of surgical treatment or gallbladder drainage according to the severity of acute cholecystitis. Consequently, the treatment methods were determined based on the general opinions of professionals. Four years have passed since the publication of the Tokyo Guidelines 2007 [2], but there are still no reliable reports of the optimal treatment for each severity grade of acute cholecystitis. The therapeutic strategy for acute cholecystitis is presented here in the question-and-answer format prepared in the revision of TG07 [2] while referring to recent reports.

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Q1. What is the optimal surgical treatment for acute cholecystitis according to the grade of severity?

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mild acute cholecystitis</td>
<td>Early laparoscopic cholecystectomy is the preferred procedure.</td>
</tr>
<tr>
<td>II</td>
<td>Moderate acute cholecystitis</td>
<td>Early laparoscopic cholecystectomy is recommended in experienced centers. However, if patients have severe local inflammation, early gallbladder drainage (percutaneous or surgical) is indicated. Because early cholecystectomy may be difficult, medical treatment and delayed cholecystectomy are necessary.</td>
</tr>
<tr>
<td>III</td>
<td>Severe acute cholecystitis</td>
<td>Urgent management of organ dysfunction and management of severe local inflammation by gallbladder drainage should be carried out. Delayed elective cholecystectomy should be performed when cholecystectomy is indicated.</td>
</tr>
</tbody>
</table>

The optimal treatment for acute cholecystitis is essentially early cholecystectomy, and the use of an established optimal surgical treatment for each grade of severity of acute cholecystitis is necessary. Early laparoscopic cholecystectomy is indicated for patients with Grade I (Mild) acute cholecystitis, because laparoscopic cholecystectomy can be performed in most of these patients. Early laparoscopic or open cholecystectomy (within 72 h after the onset of acute cholecystitis) is required in patients with Grade II (Moderate) acute cholecystitis in experienced centers, but for some patients with Grade II (Moderate) acute cholecystitis, it is difficult to remove the gallbladder surgically because of severe inflammation limited to the gallbladder. This severe local inflammation of the gallbladder is defined by factors such as >72 h from the onset, a white blood cell count >18,000, and a palpable tender mass in the right upper abdominal quadrant. Continued medical treatment or drainage of the contents of the swollen gallbladder by percutaneous transhepatic gallbladder drainage or surgical cholecystostomy is preferable, and a delayed cholecystectomy after the improvement of inflammation of the gallbladder is indicated. Among patients with Grade II (Moderate), for those with serious local complications including biliary peritonitis, pericholecystic abscess, liver abscess or for those with gallbladder torsion, emphysematous cholecystitis, gangrenous cholecystitis, and purulent cholecystitis, emergency surgery is conducted (open or laparoscopic depending on experience) along with the general supportive care of the patient. The urgent management of Grade III (Severe) acute cholecystitis is always necessary because the patients have organ dysfunction, and the simultaneous drainage of the gallbladder contents is required to treat the severe inflammation of the gallbladder. Delayed cholecystectomy is required 2 to 3 months later, after the improvement of the patients’ general condition when cholecystectomy is indicated.

Q2. Which surgical procedure is preferred, laparoscopic cholecystectomy or open cholecystectomy?

We recommend that laparoscopic cholecystectomy is preferable to open cholecystectomy (recommendation 1, level A).

Gallstones are one of the major causes of acute cholecystitis, and cholecystectomy is now being carried out in many of the patients with cholecystolithiasis. Until the first half of the 1990s, there were opinions that laparoscopic surgery was not indicated in patients with acute cholecystitis [3]. Open cholecystectomy was the standard technique. However, more recently, laparoscopic surgery has also been introduced for acute cholecystitis, and is now generally considered to be the first option for surgery, similar to open cholecystectomy. Several reports, including randomized controlled trials (RCTs) comparing laparoscopic cholecystectomy and open cholecystectomy, have indicated that laparoscopic cholecystectomy is associated with a significantly shorter postoperative hospital stay and a lower incidence of complications [4–7]. A meta-analysis has also shown that laparoscopic cholecystectomy not only resulted in treatment effects similar to those produced by open cholecystectomy, but that it is also a useful surgical procedure in terms of its low mortality and morbidity[8, 9]. However, the above reports have failed to examine its use for acute cholecystitis according to the grade of severity. Laparoscopic cholecystectomy is not recommended for all cases of acute cholecystitis due to the possibility of patients in whom cholecystectomy is difficult because of severe inflammation [10].

On the other hand, there has been a change in the perioperative management of open cholecystectomy patients in the last few years, and the current management aims to reduce postoperative pain and encourage early ambulation and early discharge. These changes show that, in terms of the postoperative course, open cholecystectomy with mini-incision is able to produce as good results as those obtained by laparoscopic cholecystectomy, although the superiority of laparoscopic cholecystectomy as a surgical technique for acute cholecystolithiasis can be recognized [8, 9]. In fact, a RCT was carried out to reappraise the use of laparoscopic cholecystectomy and open cholecystectomy by a subcostal muscle transection incision [11]. This study indicated that no significant differences were observed between the two types of cholecystectomies with regard to the rate of postoperative complications, the degree of pain at discharge, the duration of sick leave, and the direct medical
cost. At the moment, laparoscopic cholecystectomy is comprehensively preferred as the surgical treatment for acute cholecystitis. However, the first priority is the safety of the patients. With this in mind, open surgery can be considered to be as effective as laparoscopic surgery.

A cohort study was carried out in a total of approximately 30,000 patients with acute cholecystitis aged 66 years or older concerning the surgical procedures for acute cholecystitis; 75% of those patients underwent cholecystectomy at the time of the initial hospitalization, with 71% undergoing laparoscopic cholecystectomy and 29% undergoing open surgery. The results of the analysis showed that laparoscopic cholecystectomy is being used as the first option for surgical procedures that can be performed urgently for acute cholecystitis [12].

**Q3. What is the optimal timing of cholecystectomy for acute cholecystitis?**

We recommend that it is preferable to perform cholecystectomy soon after admission, particularly when less than 72 hours have passed since the onset of symptoms (recommendation 1, level A).

With regard to the timing of the surgery for acute cholecystitis, there are several reports of RCTs conducted in the 1970s and 1980s that compared early surgery and elective surgery (from the initial onset until 4 months later) by open cholecystectomy. The trials failed to find a difference between the surgical procedures in terms of the amount of bleeding, duration of surgery, and incidence of complications; however, they were able to show that early surgery is preferable because it reduces the hospital stay and leads to an early cessation of pain in the patients [12–17]. In recent years, laparoscopic cholecystectomy has been actively used for acute cholecystitis and the rate of its use has been increasing every year since its introduction [18]. The usefulness of early surgery (rather than delayed surgery) has been indicated in RCTs [19–21] and in meta-analyses in patients with acute cholecystitis [22–25]. However, the definition of early surgery differed in each report, because there were different starting times for the operations, such as onset of symptoms, time of diagnosis, and use of randomization. Early surgery was mainly conducted within 72–96 h from onset of symptoms. On the other hand, elective surgery was performed 6 weeks or more after the onset. Thus, the results of several reports indicated with a high level of evidence that laparoscopic cholecystectomy performed during the first admission was associated with a shorter hospital stay, quicker recovery, and reduction in overall medical costs compared to open cholecystectomy. Early laparoscopic cholecystectomy is now accepted to be sufficiently safe for routine use.

After evaluating a patient’s overall condition and confirmation of the diagnosis by ultrasonography, computed tomography (CT), and/or magnetic resonance cholangiopancreatography, the timing of the surgical management of acute cholecystitis patients should be decided by experienced surgeons. Unfortunately, early surgery is performed less frequently than is recommended at present because of the scarcity of surgeons [18, 26, 27]. However, the fact that the above trials excluded patients with peritonitis caused by perforation of the gallbladder, patients with common bile duct stones, and those with concomitant severe cardiopulmonary disease should be kept in mind when evaluating the results of these trials.

Additionally, each meta-analysis indicated that there was no statistically significant difference in the incidence of bile duct injury (BDI). However, these meta-analyses did not include a large enough number of patients to detect a difference, because the incidence of BDI in the laparoscopic era is generally less than 1.0% [28–30]. Therefore, it is impossible to assert that there are no significant differences in the incidence of BDI on the basis of its frequency in these meta-analyses.

**Q4. When is the optimal time for conversion from laparoscopic to open cholecystectomy?**

We recommend that surgeons should never hesitate to convert to open surgery to prevent injuries when they experience difficulties in performing laparoscopic cholecystectomy (recommendation 1, level C).

There is a relatively high rate of conversion from laparoscopic cholecystectomy to open cholecystectomy for acute cholecystitis because of technical difficulties, and laparoscopic cholecystectomy is associated with a high complication rate [10, 31]. Although preoperative factors such as male gender, previous abdominal surgery, the presence or history of jaundice, advanced cholecystitis, and infectious complications are associated with a need for conversion from laparoscopic to open cholecystectomy, they have limited predictive ability [32–34]. Surgeons assess patients using various factors when deciding whether or not conversion to open cholecystectomy, particularly during laparoscopic cholecystectomy, is necessary. Therefore, experience not only of the individual surgeons, but also of the institution where the laparoscopic cholecystectomy is conducted, is required to successfully perform cholecystectomy for all patients with acute cholecystitis.

The critical view of safety described by Strasberg et al. [1] in 1995 is of the utmost importance (Fig. 1). Above all, this critical view is now the ultimate principle for
Q5. When is the optimal time for cholecystectomy following PTGBD?

The optimal time, however, remains controversial due to a lack of any strong evidence.

There have been no randomized controlled trials that have examined the surgical management of patients with acute cholecystitis undergoing percutaneous transhepatic gallbladder drainage (PTGBD). However, PTGBD is known to be an effective option in critically ill patients, especially in elderly patients and patients with complications. Cholecystectomy is often performed following PTGBD after an interval of several days [35, 36]. However, performing a cholecystectomy 2 weeks later is also common [37]. Overall, early cholecystectomy following PTGBD is preferable when the patient’s condition improves, and if the patient has no complications. Complications of PTGBD sometimes occur, such as intrahepatic hematoma, pericholecystic abscess, biliary pleural effusion, and biliary peritonitis, which may be caused by puncture of the liver and the migration of the catheter. However, such migration should be prevented. On the other hand, PTGBA (percutaneous transhepatic gallbladder aspiration) is often used by many facilities, and produces good treatment outcomes. However, a RCT indicated that PTGBD was superior to PTGBA in terms of its clinical effectiveness [38].

Q6. What are the complications to be avoided that are associated with laparoscopic cholecystectomy?

Bile duct injury, bleeding, and the injury of other organs (level C).

Complications of laparoscopic cholecystectomy were reported soon after its introduction, and include BDI, intraperitoneal hemorrhage needing laparotomy, bowel injury, and hepatic injury, as well as the commonly observed complications associated with conventional open cholecystectomy, such as wound infection, ileus, atelectasis, deep vein thrombosis, and urinary tract infection. Bile duct injury is considered to be a serious complication. Bowel and hepatic injuries should also be carefully avoided as serious complications [28]. These injuries have been attributable to the limitations of laparoscopic procedures, such as the narrow view and non-tactile manipulation. Laparoscopic cholecystectomy is not always associated with a higher incidence rate compared with open cholecystectomy [30–32], but any serious complication that requires re-operation and/or prolonged hospitalization may become a serious problem for patients, even those who firmly believe that laparoscopic cholecystectomy is less invasive. In spite of many improvements in the technique and equipment, as well as the surgeon’s learning curve, the BDI rate remains high compared to open cholecystectomy. Table 1 shows the laparoscopic BDI rates in Japan from biannual questionnaire surveys performed by the Japan Society of Endoscopic Surgery (JSES) [28]. The incidence of BDI in the laparoscopic era is higher than that in the open cholecystectomy era, and is consistently around 0.6 %. Because of this rate, if a RCT is planned, two arms...
consisting of thousands of patients are required to detect bile duct injury. There has been no RCT consisting of such a large number of patients in individual arms. Even the arms of the meta-analyses of RCTs were not large enough to detect a difference. Therefore, it is possible that large population studies would suggest that there are some severe complications caused by laparoscopic cholecystectomy, whereas smaller studies do not indicate those problems.

We therefore performed an extensive search of the literature for all types of bile duct injury. The most extreme bile duct injury seems to be a vasculobiliary injury involving the major hepatic artery and portal vein. The incidence of extreme vasculobiliary injury is approximately 2% of the patients who sustain major biliary injuries requiring surgical reconstruction during laparoscopic cholecystectomy [39]. Such an extreme vasculobiliary injury is more likely to occur when fundus-down cholecystectomy is attempted in the presence of severe inflammation of the gallbladder, usually after the conversion from laparoscopic to open cholecystectomy. This injury is caused by dissection behind the cystic plate into the right portal pedicle. To prevent such an injury, the surgeon involved should recognize the features of severe inflammation, particularly severe contractive inflammation, and refrain from using the fundus-down technique when these symptoms are present.

Q7. When is the optimal time for cholecystectomy following endoscopic stone extraction of the bile duct in patients with cholecysto-choledocholithiasis?

Combining endoscopic stone extraction (ESE) with laparoscopic cholecystectomy during endoscopic retrograde cholangiography has been found to be a useful means of treating patients with cholecysto-choledocholithiasis. However, the optimal timing of laparoscopic cholecystectomy following ESE is still a matter of controversy in patients with acute cholecystitis. There have been several reports including meta-analysis on combinations of ESE and laparoscopic cholecystectomy for patients only without acute cholecystitis. A meta-analysis report showed that intraoperative endoscopic sphincterotomy is as effective and safe as postoperative endoscopic sphincterotomy and resulted in a significantly shorter hospital stay [40], and there were some reports which mentioned that the interval between the two procedures was a few days [41–44]. The interval between ESE and laparoscopic cholecystectomy is therefore left to the individual surgeon. At the moment, early laparoscopic cholecystectomy following ESE during the same hospital stay is preferable in some patients without complications related to ESE.

A report of an analysis of approximately 30,000 patients who were urgently admitted or admitted through the emergency department for acute cholecystitis demonstrated that a lack of definitive therapy was associated with a 38% gallstone-related cumulative readmission rate over the subsequent 2 years [12]. This report also demonstrated that patients with acute cholecystitis were more likely to have gallstone-related readmission than patients who had common bile duct stones. However, common bile duct stones are undoubtedly one of the factors predicting readmission, including gallstone-related pancreatitis [45–47]. Therefore, obtaining informed consent concerning readmission is indispensable for the possible risk for those patients who did not undergo cholecystectomy during the initial hospitalization.

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Conflict of interest

None.

References


TG13 miscellaneous etiology of cholangitis and cholecystitis

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Abstract This paper describes typical diseases and morbidities classified in the category of miscellaneous etiology of cholangitis and cholecystitis. The paper also comments on the evidence presented in the Tokyo Guidelines for the management of acute cholangitis and cholecystitis (TG 07) published in 2007 and the evidence reported subsequently, as well as miscellaneous etiology that has not so far been touched on. (1) Oriental cholangitis is the type of cholangitis that occurs following intrahepatic stones and is frequently referred to as an endemic disease in Southeast Asian regions. The characteristics and diagnosis of oriental cholangitis are also commented on. (2) TG 07 recommended percutaneous transhepatic biliary drainage in patients with cholestasis (many of the patients have obstructive jaundice or acute cholangitis and present clinical signs due to hilar biliary stenosis or obstruction).

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However, the usefulness of endoscopic naso-biliary drainage has increased along with the spread of endoscopic biliary drainage procedures. (3) As for biliary tract infections in patients who underwent biliary tract surgery, the incidence rate of cholangitis after reconstruction of the biliary tract and liver transplantation is presented. (4) As for primary sclerosing cholangitis, the frequency, age of predilection and the rate of combination of inflammatory enteropathy and biliary tract cancer are presented. (5) In the case of acalculous cholecystitis, the frequency of occurrence, causative factors and complications as well as the frequency of gangrenous cholecystitis, gallbladder perforation and diagnostic accuracy are included in the updated Tokyo Guidelines 2013 (TG13).


Keywords Oriental cholangitis · Calculous cholecystitis · Primary sclerosing cholangitis · Guidelines · Biliary infection

Introduction

Along with the addition of the evidence that has been reported since 2007, we report on the miscellaneous etiology of cholangitis and cholecystitis included in the Tokyo Guidelines for the management of acute cholangitis and cholecystitis (TG 07) [1] published in 2007. In view of the presence of miscellaneous evidence that has not so far been touched on, we thought it necessary that the updated Tokyo Guidelines 2013 (TG13) prepare new items, put the evidence so far collected in its due place, and provide explanations. Diseases and morbidities classified in this category include (1) oriental cholangitis, (2) acute cholangitis and cholecystitis associated with pancreaticobiliary malignancies, (3) biliary tract infections in patients who underwent previous biliary tract surgery, (4) primary sclerosing cholangitis, and (5) acalculous cholecystitis.

In this paper, we present comments not only on the characteristics of miscellaneous etiology of cholangitis and cholecystitis but also on diagnostic and therapeutic methods, along with the addition of the newly reported evidence.

Oriental cholangitis (cholangiohepatitis)

Characteristics

Oriental cholangitis (Fig. 1, Supplement Fig. 1) is defined as that type of cholangitis characterized by recurrent right upper quadrant pain, fever, chill and jaundice induced by intrahepatic biliary stricture and intrahepatic stones. It is a pandemic disease observed in Southeast Asian regions, and people in the low-income group are frequently affected by the disease. Involvement of $\beta$-glucuronidase due to parasitic and bacterial biliary tract infections is suggested as a causative factor [2–7]. In recent years, however, it is rare that the presence of parasites is confirmed by a resected specimen of the liver [8]. Terms such as “oriental cholangitis,” “recurrent pyogenic cholangitis” and “primary hepatolithiasis” are frequently used in Korea, Hong Kong and Japan. They have been referred to as the terms that describe different aspects of the same morbidities [9]: emphasis is placed on ethnic predilection and the mysterious nature of “oriental cholangitis”, clinical presentation and suppurrative inflammation in “recurrent pyogenic cholangitis”, and pathological changes in “primary hepatolithiasis”, respectively [9]. Pathologically, “oriental cholangitis” is characterized by dilatation and stricture of the extrahepatic/intrahepatic bile duct accompanying intrahepatic pigment calculi, and hypertrophy is observed in the bile duct wall accompanied by intrahepatic pigment calculus and thickening accompanied by fibrosis and inflammatory cell invasion [2–5, 7].

As for parasites related to oriental cholangitis, roundworms and Chinese liver flukes have been reported. Adult
roundworms sometimes enter the bile duct through the duodenal papilla and give rise to cholangitis in 16–56.6% of patients [10]. Chinese liver flukes colonize the intrahepatic bile duct and then live there for 20–30 years, causing chronic inflammatory parasitic changes [11].

Q1. What are the imaging findings of oriental cholangitis?

The imaging findings of oriental cholangitis are follows; extrahepatic bile duct dilatation, intrahepatic calculi, localized dilatation/stricture in the biliary tree of the medial segment of the liver, atrophy of the liver segment/decreased blood flow, increased echogenicity (US) of the hepatic portal vein, and liver abscess.

Diagnosis

Ultrasound/computed tomography (US/CT) enables observation of bile duct dilatation and pneumobilia (Fig. 1, Supplement Fig. 1), increased US echogenicity in the portal vein segment of the liver, and atrophy of the liver segment/decreased blood flow [4–6, 8]. However, US does not necessarily depict intrahepatic stones accompanied by acoustic shadow [8]. Calcium bilirubinate calculi are also observed as a high-absorption region on CT; however, due to the low absorption level of cholesterol stones, depiction of cholesterol stones sometimes becomes difficult [8]. Magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) is able to provide better imaging without the risk of aggravated sepsis cholangitis and is good at depicting lesions on the proximal side of the obstruction and structure and those outside of the biliary duct [6]. However, when cholestasis is present, a diagnosis of stones can become impossible or it may be impossible to visualize the bile duct because of bile concentration and low signal. Pneumobilia is likely to be mistaken for stones because it presents a low signal [8]. The rate of correct diagnosis of the obstructed location by MRI/MRCP is 96–100%, a diagnosis of a cause of obstruction is made in 90% and one of intrahepatic stones is the same as that by endoscopic retrograde cholangiopancreatography (ERCP). Direct cholangiography such as percutaneous transhepatic cholangiography is an invasive test [6] and it has merits in that it simultaneously enables (1) the removal of intrahepatic stones, (2) biopsy of bile duct lesions, and (3) stent placement in the bile duct [8]. The reported imaging findings from direct cholangiography are those of the dilated bile duct and stones, straightening of the bile duct, rigidity, decreased arborization, increased branching angle, acute peripheral tapering and multiple focal strictures [5, 6]. The diagnostic sensitivity of direct cholangiography for making a diagnosis of bile duct obstruction is 100%, that for stones is somewhat inferior to that of MRCP (90–96%), and specificity is 98%. The incidence of liver abscess in oriental cholangitis is 20% lower; there is often a number of partitions. Abscess should therefore be suspected when the limbus is depicted with CT [6].

Acute cholangitis and cholecystitis associated with pancreaticobiliary malignancy

Characteristics

Biliary drainage is carried out for pancreaticobiliary malignancies because they are frequently accompanied by obstructive jaundice. However, patients with morbidities accompanied by acute cholangitis requiring urgent biliary drainage are few in number (Supplement Fig. 2). Acute cholangitis requiring urgent biliary drainage is frequently observed in the following patients: (1) those who failed to undergo biliary drainage even if the bile duct at the upper stream of the liver above the obstructed site of the bile duct was depicted, and (2) those in whom drainage was unsuccessful due to catheter obstruction even though a drainage tube had been placed in the bile duct at the upper stream of the liver above the obstructed site of the bile duct due to malignant tumor [1].

The destruction of papillary function due to stent placement and re-obstruction of the bile duct arising from tumor enlargement have been reported as a risk factor for acute cholangitis after metal stent placement for internal...
biliary drainage. Furthermore, cancer progression to the cystic duct and cystic duct obstruction due to stent replacement in the bile duct have been reported as risk factors for the development of acute cholecystitis after stent placement [12–15].

Diagnosis

As for the diagnostic accuracy of diagnostic imaging for malignant tumors, there is a report showing that the sensitivity/specificity/rate of correct diagnosis of US for extrahepatic bile duct cancers are 85.6/76.9/84.4 % for cancers of the hilar bile duct; 59.1/50/57.1 % for cancers of the middle bile duct; and 33.3/42.8/36.8 % for cancers of the lower bile duct, respectively [16]. There are reports showing that about 100 % of the tumors of the biliary system, except early cancers, are recognized with multidetector CT and a judgment of the usefulness of resection can be made in 74.5–91.7 % of the cases [17, 18]. A meta-analysis of MRCP has found that its sensitivity and specificity are 97/88 and 98/95 %, respectively, when the detection of obstruction/malignancy has been set as the end point [19].

Q2. How drainage should be carried out for postoperative acute cholangitis following pancreaticobiliary malignancies?

We suggest a safe and reliable method should be selected at the facility concerned. When it is difficult, emergency transportation to an appropriate facility should take place (recommendation 1, level C).

Treatment

The presence of preoperative cholangitis and cholecystitis without control of pancreaticobiliary malignancies is an independent risk factor for postoperative death during hospital stay and the development of complications, so it is considered that the control of those morbidities is important [20–23]. In recent years, we have occasionally come across opinions that recommend the use of endoscopic naso-biliary drainage for hilar cholangiocarcinoma also, in view of the occurrence of vascular injuries (8 %), peritoneal dissemination (4 %) and recurrence of fistula (5.2 %) [24, 25]. However, there are so far no reports of randomized controlled trials comparing the modalities of preoperative biliary drainage. Therefore, it is thought that what matters at this time will be whether or not there are physicians expert in endoscopic or percutaneous drainage at the facility involved, and the selection of a method enabling safe and reliable emergency biliary drainage [26]. When the above conditions are not applicable, patients should be transferred to an appropriate facility to undergo biliary drainage.

Due to possible risks associated with preoperative percutaneous biliary drainage for fistula recurrence and carcinomatous peritonitis [1], one-stage radical surgery should be conducted as far as the circumstances allow.

Biliary tract infections in patients who have undergone previous biliary tract surgery

Q3. What is the frequency of cholangitis after biliary tract reconstruction?

Cholangitis occurs in about 10 % of the patients after biliary tract reconstruction.

Characteristics

After ERCP and biliary tract surgery, there can be latent cholangitis and cholecystitis. According to reports that have examined patients undergoing biliary tract reconstruction, cholangitis occurred during 29–129 months’ follow-up in 11.3 % of the patients after papilloplasty, 10.3–10.9 % after choledochoduodenostomy, and 6.4–11.3 % after choledochojejunostomy (Supplement Fig. 3), and in about 4 % of patients in whom cholangitis was recurrent and severe [27, 28]. Although there are no differences between perioperative mortality rate and the incidence rate of complications [28], bile duct carcinomas occurred after biliary tract reconstruction in 1.9–7.6 % of the patients, suggesting the presence of a relationship between inflammatory changes in the bile duct following biliary tract reconstruction and biliary tract cancer that occurs in the late stage [27]. According to a report on patients who were followed up for more than 10 years after surgery for congenital biliary tract dilatation conducted in childhood (mean age 4.2 years), impairment of the liver occurred in 10.7 % of the patients, bile duct dilatation in 10.7 %, and repeated cholangitis in 1.8 % [29].

A systematic review of liver transplantation in adult patients shows that bile duct stricture occurred in 12 % of patients undergoing brain-dead donor liver transplantation and in 19 % of patients undergoing live-donor liver transplantation [30]. According to a discussion of the result according to the surgical techniques of biliary tract reconstruction in 51 patients who had undergone liver transplantation due to primary sclerosing cholangitis (PSC), there were no differences in the survival rate in
patients who had undergone choledochoduodenostomy, choledochojunostomy or choledochocholedochostomy. However, the incidence of postoperative biliary tract complications that had occurred more than once was 48, 60 and 17 %, respectively [31].

It is reported that the incidence of cholecystitis differs (0.06–12.6 %) according to underlying diseases other than biliary tract surgery or surgical techniques and that the frequency of acalculous cholecystitis is high [32–37].

Primary sclerosing cholangitis

Characteristics

Primary sclerosing cholangitis (PSC) (Fig. 2) causes stricture and obstruction due to progressive and non-specific inflammation of the intra- and extrahepatic bile duct wall and progresses from cholestasis to liver cirrhosis and hepatic failure. Its etiology remains unknown [38, 39]. It is therefore important that secondary sclerosing cholangitis is excluded [40]. PSC is frequently observed in males, Caucasians and Northern Europeans [38]; the incidence rate is 0.41–1.25 patients/100,000 person-years [41, 42], and the mean age at onset is 42 years [38]. There are reports that the age distribution is bipolar in shape with one peak at the 20s and another peak between the 50s and 60s [43, 44]. It is classified into the following 4 stages: (1) small duct cholangitis, (2) progressive cholestasis, (3) cirrhosis, and (4) decompensation [38, 45]. Clinical symptoms differ according to the stage of the disease. It is detected by blood test and is often asymptomatic [44]. When the disease has progressed, cutaneous pruritus following cholestasis, jaundice, fever due to cholangitis, and abdominal pain occur. A combination of inflammatory intestinal disease and biliary tract cancer occurs in 4.3–16.6 % of PSC cases [41, 42, 44, 46–51].

Diagnosis

ERCP is a standard imaging test. MRCP has shown promise in recent years as a minimally invasive imaging test procedure [38]. Imaging findings in the bile duct include band-like stricture, beaded appearance (Fig. 2), pruned tree-like appearance, and diverticulum-like outpouching [52]. The Mayo Clinic diagnostic criteria, which are widely used [40] (Supplementary Table 1), make much of the imaging findings of intra/extrahepatic bile duct stricture and the biliary tract. Elevated levels of serum ALP and T-Bil and an increased leukocyte count are findings common to acute cholangitis. An increased eosinophilic count, a serum γ-globulin level, an elevated IgG/IgM level, positive anti-nuclear antibody and positive perinuclear antineutrophil cytoplasmic antibody (p-ANCA) are useful for differentiation from acute cholangitis. An increased eosinophilic count, a serum γ-globulin level, an elevated IgG/IgM level, positive anti-nuclear antibody and positive perinuclear antineutrophil cytoplasmic antibody (p-ANCA) are useful for differentiation from acute cholangitis [38, 43, 44]. The positive rates are ALP 88 %, ALT 73 %, T-Bil 39 %, P-ANCA 7–77 %, and anti-nuclear antibody 33–87 % [38, 44]. According to meta-analyses, MRCP shows 86 % diagnostic sensitivity and 94 % specificity, demonstrating that it is somewhat inferior in terms of the depiction of the intra/extrahepatic bile duct and a diagnosis of liver cirrhosis and cancer at the early stage [53, 54]. However, it is considered that MRCP has sufficient capacity to enable a diagnostic test for various types of diseases [55]. A diagnosis of cholangiocarcinoma occurring in PSC patients without tumor formation remains a challenging task, so the diagnosis of cholangiocarcinoma is made comprehensively by means of diagnostic modalities such as CA19-9, diagnostic imaging and scraping cytology [56–59]. It is reported that the diagnostic sensitivity/specificity of US, CT and MRI for cholangiocarcinoma are about 57/94, 75/80, 63/79 %, respectively [58]. There is a report showing that positron emission tomography (PET)-CT is useful for making a diagnosis of cholangiocarcinoma [49]. On the other hand, there are also reports showing that PET-CT is not useful [60]. Concomitant use of intra- ductal ultrasound is reported to be associated with the elevated sensitivity and specificity of endoscopic retrograde cholangiography [61, 62]. The sensitivity and specificity of scraping cytology for the bile duct are reported to be about 18–73 and 95–100 %, respectively [56, 59, 63, 64].
Acalculous cholecystitis

Characteristics

Patients with acute acalculous cholecystitis (Fig. 3) account for 3.7–14 % of the patients with acute cholecystitis, 12–49 % of which occurs after trauma and major surgery [65, 66]. Acute acalculous cholecystitis occurs in about 1 % of patients admitted to intensive care units (ICUs) [67], about 1.2 % of patients with severe burns [68], 59–63 % of patients with gangrenous cholecystitis, and 15–20 % of patients with gallbladder perforation [65, 69–71] together with frequent multiple organ dysfunction. The mortality rate is 0 % when the patient’s general status is maintained [65, 72]; however, it is high (30–53 %) in critically ill patients [67–69]. Early and appropriate diagnosis and treatment are necessary to reduce the mortality rate [69, 71]. Risk factors for the development of acalculous cholecystitis include surgery, trauma, long-term ICU stays, infections, burns and parenteral nutrition [67, 68]. It is reported that ischemia, reperfusion injury and proinflammatory mediators such as eicosanoids are involved in the mechanisms for developing such conditions [69, 73].

Diagnosis

Patients are under respiratory control and frequently develop consciousness disturbance arising from the use of analgesics. Findings such as an elevated leukocyte count, liver function disorder and clinical symptoms such as sonographic Murphy’s sign, right hypochondriac pain and fever that are highly specific for acute calculous cholecystitis are not specific for acute acalculous cholecystitis [66, 71]. US/CT findings include thickening of the wall (>3.5 mm), pericholecystic fluid, emphysematous gallbladder, sloughed mucosal membrane, and lack of gallbladder wall enhancement (only for CT). The sensitivity/specificity of US are 30–92/89–100 %, and those of CT are 33–100/99–100 % [70, 74, 75]. When HIDA (hepatobiliary iminodiacetic acid) scan fails to visualize the gallbladder, the case is judged positive. The sensitivity and specificity of HIDA scan are 68–100 and 38–100 %.

![Fig. 3 Acalculous acute cholecystitis: dynamic CT (a-c) shows gallbladder distention, mucosal enhancement (b, c arrows), and transient pericholecystic liver enhancement (b arrowheads). MRCP (d) shows gallbladder distension. Gallbladder shows marked hyperintensity (asterisk) on fat-suppressed T1-weighted MR image (e) and T2-weighted image (f) indicating inspissated bile juice](https://example.com/figure3.png)
respectively. HIDA scan is likely to detect positive cases depending on complications (intravenous hyperalimentation, fasting, hepatic failure) [71]. The rate of correct diagnosis of diagnostic laparoscopy in critically ill patients is reported to be 90–100% [76].

Q4. What treatment is being carried out for acute acalculous cholecystitis?

Cholecystectomy and/or cholecystostomy (drainage of the GB) are being conducted.

Treatment

Cholecystectomy and/or cholecystostomy (drainage of the gallbladder) are carried out. However, appropriate timing and necessity of cholecystectomy and cholecystostomy are controversial [71]. There are many opinions that cholecystectomy should be conducted in patients with poor general status and that cholecystostomy should be carried out after recovery has been achieved [69, 71, 77, 78]. However, there is a group arguing that cholecystectomy only should be performed [79] and a group asserting that cholecystostomy is the definitive treatment in patients with extremely high risk [80].

Conflict of interest  None.

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Newsletter, January 1, 2013

A-P HPBA activities

Dear Colleagues,

As the founding president of the Asian-Pacific HPBA, I would like to underline once again that this journal is the official journal of the following three societies:

- The Asian-Pacific Hepato-Pancreato-Biliary Association (A-P HPBA)
- The Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS)
- The Japan Biliary Association (JBA)

It is my pleasure to inform you of the current activities of the Asian-Pacific Hepato-Pancreato-Biliary Association (A-P HPBA).

Third Congress of Asian-Pacific HPBA

The Third Biennial Congress, 2011 A-P HPBA, was held in Melbourne, Australia, 27–30 September 2011 and was chaired by Professor Christopher Christophi.

The 2011 Congress focused on “making a difference with new technologies” and provided an exciting and innovative scientific program in a unique destination—Melbourne, Australia.

There were postgraduate courses held on 27 September, followed by three packed days from 28 to 30 September with a variety of different presentation types including symposia, debates, video sessions, and case presentations. To supplement the scientific program, the Congress social events provided an ideal opportunity for networking with colleagues and industry associates in an atmosphere of typical Melbourne hospitality.

Fourth Congress of Asian-Pacific HPBA

The Fourth Biennial Congress, 2013 A-P HPBA, will take place in Shanghai, China, 27–30 March 2013 with Professor Meng Chao Wu at the helm.

The theme for the A-PHPBA2013 Shanghai Congress will be “Seeking Common Ground While Reserving Differences”. This Congress will be unique as our Scientific Committee has prepared an outstanding program combining the best science and education. It will comprise pre-congress postgraduate courses and a variety of symposia, debates, video sessions, and case presentations. As China’s largest city, Shanghai is an outstanding conference destination, located at the hub of this ancient country. There will be no shortage of activities for delegates and accompanying persons.
Please visit the Congress website http://www.aphpba2013shanghai.org, where you will find further information.

We look forward to welcoming you to Shanghai in 2013, and we are confident that the event will be a memorable occasion for exchanging knowledge and strengthening friendship.

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