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Background: Tokyo Guidelines for the management of acute cholangitis and cholecystitis

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Abstract
There are no evidence-based-criteria for the diagnosis, severity assessment, of treatment of acute cholecysitis or acute cholangitis. For example, the full complement of symptoms and signs described as Charcot's triad and as Reynolds' pentad are infrequent and as such do not really assist the clinician with planning management strategies. In view of these factors, we launched a project to prepare evidence-based guidelines for the management of acute cholangitis and cholecystitis that will be useful in the clinical setting. This research has been funded by the Japanese Ministry of Health, Labour, and Welfare, in cooperation with the Japanese Society for Abdominal Emergency Medicine, the Japan Biliary Association, and the Japanese Society of Hepato-Biliary-Pancreatic Surgery. A working group, consisting of 46 experts in gastroenterology, surgery, internal medicine, emergency medicine, intensive care, and clinical epidemiology, analyzed and examined the literature on patients with cholangitis and cholecystitis in order to produce evidence-based guidelines. During the investigations we found that there was a lack of high-level evidence, for treatments, and the working group formulated the guidelines by obtaining consensus, based on evidence categorized by level, according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence of May 2001 (version 1). This work required more than 20 meetings to obtain a consensus on each item from the working group. Then four forums were held to permit examination of the Guideline details in Japan, both by an external assessment committee and by the working group participants (version 2). As we knew that the diagnosis and management of acute biliary infection may differ from country to country, we appointed a publication committee and held 12 meetings to prepare draft Guidelines in English (version 3). We then had several discussions on these draft guidelines with leading experts in the field throughout the world, via e-mail, leading to version 4. Finally, an International Consensus Meeting took place in Tokyo, on 1–2 April, 2006, to obtain international agreement on diagnostic criteria, severity assessment, and management.

Key words Cholangitis · Cholecystitis · Charcot's triad · Reynold's pentad · Biliary drainage

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Introduction

No guidelines focusing on the management of biliary infection (cholangitis and cholecystitis) have previously been published, and no worldwide criteria exist for diagnostic and severity assessment. "Charcot's triad"[1] is still used for the diagnosis of acute cholangitis. How-

ever, these criteria were first proposed in 1877 (level 4), more than 100 years ago. Here, and throughout the series, levels of evidence are stated for referenced articles in accordance with the Oxford Centre for Evidence-Based Medicine Levels of Evidence of May 2001 (see Table 1). However only 50%–70% of cholangitis patients present clinically with Charcot's triad.[2–8] In addition, Murphy's sign[9] (level 5) is useful (sensitivity of 50%–70% and specificity of 79%–96%) in diagnosing cholecystitis, and this sign is widely used in every country. Moreover, as many of the symptoms and concepts of these diseases referred to in textbooks and reference books vary from those originally stated, the issue of worldwide criteria is problematic. In view of these unfavorable situations, we considered it necessary to clarify the definitions, concepts of disease, and treatment methods for acute cholangitis and acute cholecystitis and establish universal criteria that can be widely recognized and used.

A working group to establish practical Guidelines for the Management of Cholangitis and Cholecystitis was organized in 2003 (chief researcher, Tadahiro Takada). This project was funded by a grant from the Japanese Ministry of Health, Labour, and Welfare, and was supported by the Japanese Society for Abdominal Emergency Medicine, the Japan Biliary Association, and the Japanese Society of Hepato-Biliary-Pancreatic Surgery. The working group consisted of physicians engaged in gastroenterology, internal medicine, surgery, emergency medicine, intensive care, and clinical epidemiology as the main members, and they started the work to prepare the Guidelines.

As the research progressed, the group was faced with the serious problem that high-level evidence regarding the treatment of acute biliary infection is poor. Therefore, an exective committee meeting was convened, and the committee came to the following decision: the Guidelines would be evidence-based in general, but areas without evidence or with poor evidence (such as diagnosis and severity assessment) should be completed by obtaining high-level consensus among experts worldwide.

We established a publication committee and held 12 meetings to prepare draft Guidelines in English (version 3). Then we had several discussions on these draft Guidelines with leading experts in the field throughout the world, via e-mail, leading to version 4. Finally, an International Consensus Meeting took place in Tokyo, on 1–2 April, 2006, to obtain international agreement on diagnostic criteria, severity assessment, and management.

We now publish the "Tokyo Guidelines for the Management of Cholangitis and cholecystitis". These Guidelines consist of 13 articles, including "Discussion" sections containing comments of attendees at the consensus conference and analyses of audience voting at the meeting.

We hope that these Guidelines will help their users to give optimal treatment according to their own specialty and capability, and thus provide their patients with the best medical treatment.

Background of Tokyo Guidelines

Biliary infections (acute cholangitis and cholecystitis) require appropriate management in the acute phase. Serious acute cholangitis may be lethal unless it is appropriately managed in the acute phase. On the other hand, although various diagnostic and treatment methodologies have been developed in recent years, they have not been assessed objectively and none of them has been established as a standard method for the management of these diseases. We carried out an extensive review of the English-language literature and found that there was little high-level evidence in this field, and no systematically described practical manual for the field. Most importantly, there are no standardized diagnostic criteria and severity assessments for acute cholangitis and cholecystitis, therefore, we would like to establish standards for these items. The Tokyo Guidelines include evidence-based medicine and reflect the international consensus obtained through earnest discussions among professionals in the field on 1–2 April, 2006, at the Keio Plaza Hotel, Tokyo, Japan. Concerning the definitions in the practice guidelines, we have applied to the Japanese Institute of Medicine: Committee to Advise the Public Health Service on Clinical Practice Guidelines, to approve the systematically developed Guidelines to assist practioner and patient decisions about appropriate healthcare for specific clinical circumstances.

Notes on the use of the Guidelines

The Guidelines are evidence-based, with the grade of recommendation also based on the evidence. The Guidelines also present the diagnostic criteria for and severity assessment of acute biliary infection. As the Guidelines address so many different subjects, indices are included at the end for the convenience of readers.

The practice Guidelines promulgated in this work do not represent a standard of practice. They are suggested plans of care, based on best available evidence and the consensus of experts, but they do not exclude other approaches as being within the standard of practice. For example, they should not be used to compel adherence to a given method of medical management, which meth-

od should be finally determined after taking account of the conditions at the relevant medical institution (staff levels, experience, equipment, etc.) and the characteristics of the individual patient. However, responsibility for the results of treatment rests with those who are directly engaged therein, and not with the consensus group. The doses of medicines described in the text of the Guidelines are for adult patients.

Methods of formulating the guidelines

With evidence-based medicine (EBM) as a core concept, the Guidelines were prepared by the Research Group on the Preparation and Diffusion of Guidelines for the Management of Acute Cholangitis and Acute Cholecystitis (chief researcher, Tadahiro Takada), under the auspices of the Japanese Ministry of Health, Labour, and Welfare, and the Working Group for Guideline Preparation, whose members were selected from experts in abdominal emergency medicine and epidemiology by the Japanese Society for Abdominal Emergency Medicine, the Japan Biliary Association, and the Japanese Society of Hepato-Biliary-Pancreatic Surgery.

In principle, the preparation of the Guidelines progressed with the systematic search, collection, and assessment of references for the objective extraction of evidence. Next, the External Assessment Committee examined the Guidelines. Then we posted the draft guidelines on our website and had four open symposia, bginning in September 2004, to gain feedback for further review. Subsequently, a Publication Committee was set up, and this committee had 12 meetings to prepare draft Guidelines.

Re-examination of the draft Guidelines was then performed, via e-mail, with experts on cholangitis and cholecystitis throughout the world. After final agreement was reached at the International Consensus Meeting, held in Tokyo in April 2006, "the Tokyo Guidelines for the Management of Acute Cholangitis and Cholecystitis" were completed.

The process of extending the literature search

The literature was selected as follows: Using "cholangitis" and "cholecystitis" as the medical subject heading (MeSH; explode) or the key search words, approximately 17200 items were selected from Medline (Ovid; 1966 to June 2003). These articles were subjected to a further screening with "human" as the "limiting word". This screening provided 9618 items in English and in Japanese. A further 7093 literature publications were obtained from the Japana Centra Revuo Medicina (internet version), using "cholangitis", "cholecystitis", and "biliary infection" as the key words, with further screening with "human" as the "limiting word". This process provided 6141 items. After the titles and abstracts of a total of 15759 works were examined by two committee members, 2494 were selected for a careful examination of their full texts.

Other literature quoted in these selected works, together with works suggested by the specialist committee members, were included in the examination.

To evaluate each article, a STARD (standards for reporting of diagnostic accuracy) checklist (Table 1)[12] was considered important. The purpose of this checklist is to evaluate the format and study process, in order to improve the accuracy and completeness of the reporting of studies of diagnostic accuracy.

However, the STARD checklist is not suitable for classifying various categories (e.g., therapy, prevention, etiology, harm, prognosis, diagnosis, differential diagnosis, economic and decision analysis) and levels of evidence. Therefore, in the Guidelines, the science-based classification used by the Cochrane Library (Table 2) was adopted.

The evidence obtained from each item of reference was evaluated in accordance with the science-based classification used by the Cochrane Library (Table 2), and the quality of evidence for each parameter associated with the diagnosis and treatment of acute biliary infection was determined. As stated above, the level of evidence presented by each article was determined in accordance with the Oxford Centre for Evidence-Based Medicine Levels of Evidence (May 2001), prepared by Phillips et al.[13] (Table 2). The terms used in the categories are explained in the footnote to Table 2.

Categories of evidence and grading of recommendations

Based on the results obtained from these procedures, grades of recommendation were determined, according to the system for ranking recommendations in clinical guidelines[14–16] shown in Table 3, and mentioned, as required, in the text of the Guidelines. The grades of recommendation in the Guidelines are based on the Kish[14] method of classification and others.[15,16] Recommendations graded "A" (that is, "do it") and "B" (that is, "probably do it"), are based on a high level of evidence, whereas those graded "D" (that is, "probably don't do it") or "E" (that is, "don't do it") reflect a low level of evidence.

Acknowledgments. We would like to express our deep gratitude to the Japanese Society for Abdominal Emergency Medicine, the Japan Biliary Association, and the Japanese Society of Hepato-Biliary-Pancreatic Surgery, who provided us with great support and guidance in the preparation of the Guidelines. This process was conducted as part of the project for the Preparation and

Table 1. STARD checklist for the reporting of studies of diagnostic accuracy

Section and topic	Item no.		On page no.
Title/Abstract/ Key words	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading "sensitivity and specificity")	
Introduction	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups	
Methods		Describe	
Participants	3	The study population: the inclusion and exclusion criteria, setting and locations where the data were collected	
	4	Participant recruitment: was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	
	5	Participant sampling: was the study population a consecutive series of participants defined by the selection criteria in items 3 and 4? If not, specify how participants were further selected	
	6	Data collection: was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	
Test methods	7	The reference standard and its rationale	
	8	Technical specifications of material and methods involved, including how and when measurements were taken, and/or cite references for index tests and reference standard	
	9	Definition of and rationale for the units, cutoffs, and/or categories of the results of the index tests and the reference standard	
	10	The number, training, and expertise of the persons executing and reading the index tests and the reference standard	
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test, and describe any other clinical information available to the readers	
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g., 95% confidence intervals)	
	13	Methods for calculating test reproducibility, if done	
Results		Report	
Participants	14	When study was done, including beginning and ending dates of recruitment	
	15	Clinical and demographic characteristics of the study population (e.g., age, sex spectrum of presenting symptoms, comorbidity, current treatments, recruitment centers)	
	16	The number of participants satisfying the criteria for inclusion that did or did not undergo the index tests and/or the reference standard; describe why participants failed to receive either test (a flow diagram is strongly recommended)	
Test results	17	Time interval from the index tests to the reference standard, and any treatment administered between	
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition	
	19	A cross-tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard	
	20	Any adverse events from performing the index tests or the reference standard	
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g., 95% confidence intervals)	
	22	How indeterminate results, missing responses, and outliers of the index tests were handled	
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers, or centers, if done	
	24	Estimates of test reproducibility, if done	
Discussion	25	Discuss the clinical applicability of the study findings	

Adapted from reference 12
MeSH, medical subject heading; STARD, standards for reporting of diagnostic accuracy

Table 2. Categories of evidence (refer to levels of evidence and grades of recommendations on the homepage of the Centre for Evidence-Based Medicine)

The science-based classification used by the Cochrane Library: Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001) (http://www.cebm.net/levels_of_evidence.asp#levels)[13] was used as a basis to evaluate evidence presented in each article; the quality of evidence for each parameter associated with the diagnosis and treatment of acute cholangitis and acute cholecystitis was determined

Level	Therapy/prevention, aetiology/harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity[a]) of RCTs	SR (with homogeneity[a]) of inception cohort studies; CDR[b] validated in different populations	SR (with homogeneity[a]) of level 1 diagnostic studies; CDR[b] with 1b studies from different clinical centers	SR (with homogeneity[a]) of prospective cohort studies	SR (with homogeneity[a]) of level 1 economic studies
1b	Individual RCT (with narrow confidence interval[c])	Individual inception cohort study with >80% follow-up; CDR[b] validated in a single population	Validating[d] cohort study with good[e] reference standards; or CDR[b] tested within one clinical center	Prospective cohort study with good follow-up[f]	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none[g]	All or none case-series	Absolute SpPins and SnNouts[h]	All or none case-series	Absolute better-value or worse-value analyses[i]
2a	SR (with homogeneity[a]) of cohort studies	SR (with homogeneity[a]) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity[a]) of level >2 diagnostic studies	SR (with homogeneity[a]) of 2b and better studies	SR (with homogeneity[a]) of level >2 economic studies
2b	Individual cohort study (including low-quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR[b] or validated on split-sample[j] only	Exploratory[d] cohort study with good[e] reference standards; CDR[b] after derivation, or validated only on split-sample[j] or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" research; ecological studies	"Outcomes" research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity[a]) of case-control studies		SR (with homogeneity[a]) of 3b and better studies	SR (with homogeneity[a]) of 3b and better studies	SR (with homogeneity[a]) of 3b and better studies
3b	Individual case-control study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor-quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations

Table 2. *Continued*

Level	Therapy/prevention, aetiology/harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
4	Case-series (and poor-quality cohort and case-control studies[k])	Case-series (and poor-quality prognostic cohort studies[l])	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opi\nion without explicit critical appraisal, or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Users can add a minus-sign "–" to denote the level that fails to provide a conclusive answer because of: EITHER a single result with a wide confidence interval (such that, for example, an ARR in an RCT is not statistically significant but whose confidence intervals fail to exclude clinically important benefit or harm) (Note #1), OR a systematic review with troublesome (and statistically significant) heterogeneity (Note #2). Such evidence is inconclusive, and therefore can only generate grade D recommendations (Note #3)
SR, Systematic review; RCT, Randomized controlled trial; ARR, absolute risk reduction
[a] By homogeneity, we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "–" at the end of their designated level
[b] Clinical decision rule. These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category
[c] See note #2 for advice on how to understand, rate, and use trials or other studies with wide confidence intervals
[d] Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g., using a regression analysis) to find which factors are "significant"
[e] Good reference standards are independent of the test, and are applied blindly or objectively to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a nonindependent reference standard (where the "test" is included in the "reference", or where the "testing" affects the "reference") implies a level 4 study
[f] Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (e.g., 1–6 months, acute; 1–5, years, chronic)
[g] Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it
[h] An "absolute SpPin" is a diagnostic finding whose specificity is so high that a positive result rules-in the diagnosis. An "absolute SnNout" is a diagnostic finding whose sensitivity is so high that a negative result rules-out the diagnosis
[i] Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and equally or more expensive
[j] Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples
[k] By poor-quality cohort study, we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and nonexposed individuals, and/or failed to identify or appropriately control known confounders, and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor-quality case-control study, we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders
[l] By poor-quality prognostic cohort study, we mean one in which sampling was biased in favor of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, nonobjective way, or there was no correction for confounding factors
Good, better, bad, and worse refer to the comparisons between treatments in terms of their clinical risks and benefits

Table 3. Grading system for ranking recommendations in clinical guidelines[14–16]

Grade of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation, or the effect may not exceed the adverse effects and/or inconvenience (toxicity, interaction between drugs and cost)
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use

Diffusion of Guidelines for the Management of Acute Cholangitis (H-15-Medicine-30), with a research subsidy for fiscal 2003 and 2004 (Integrated Research Project for Assessing Medical Technology) sponsored by the Japanese Ministry of Health, Labour, and Welfare.

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Discussion at the Tokyo International Consensus Meeting

Tadahiro Takada (Japan): "Dr. Strasberg, please explain the difference between a 'Guidelines' and 'Standards' in your mind?"

Steven Strasberg (USA): "To me, 'guidelines' represent a suggested course of action based on available evidence. They do not imply that other courses of action are below an acceptable level of care. Practice 'standards' are different, in that they imply that actions other than those listed as acceptable practice standards are below the level of acceptable care. It is particularly true that, in an area in which high levels of evidence are not available, that guidelines are not construed to be standards. Reliance on expert opinion to form guidelines may be useful, but even a consensus of experts may not be correct. For this reason a statement of the following type should be inserted in the introduction. 'The practice guidelines promulgated in this work do not represent a standard of practice. They are a suggested plan of care based on best available evidence and a consensus of experts, but they do not exclude other approaches as being within the standard of practice'."

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

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

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

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Introduction

Acute biliary infection is a systemic infectious disease which requires prompt treatment and has a significant mortality rate.[1] The first report on acute biliary infection was Charcot's "The symptoms of hepatic fever" in 1877.[2]

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

Acute cholangitis

Definition

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

Historical aspects of terminology

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

Acute obstructive cholangitis. Acute obstructive cholangitis was defined by Reynolds and Dargan[3] in 1959 as a syndrome consisting of lethargy or mental confusion and shock, as well as fever, jaundice, and abdominal pain, caused by biliary obstruction. They indicated that emergent surgical biliary decompression was the only effective procedure for treating the disease. These five symptoms were then called Reynolds's pentad.

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

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

Incidence

Etiology

Acute cholangitis requires the presence of two factors: (1) biliary obstruction and (2) bacterial growth in bile (bile infection). Frequent causes of biliary obstruction are choledocholithiasis, benign biliary stenosis, stricture of a biliary anastomosis, and stenosis caused by malignant disease (level 4).[5,6] Choledocholithiasis used to be the most frequent cause of the obstruction, but recently, the incidence of acute cholangitis caused by malignant disease, sclerosing cholangitis, and non-surgical instrumentation of the biliary tract has been increasing. It is reported that malignant disease accounts for about 10%–30% of cases of acute cholangitis. Tables 1 and 2 show some results of studies on the causes of acute cholangitis.

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

Table 1. Etiology of acute cholangitis

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

Table 2. Causes of acute cholangitis (%)

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

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

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

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

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

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

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

Pathophysiology

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

Prognosis

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

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

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

Acute cholecystitis

Definition

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

Incidence

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

Etiology

Cholecystolithiasis accounts for 90%–95% of all causes of acute cholecystitis, while acalculous cholecystitis accounts for the remaining 5%–10% (level 4).[41–47]

Table 3. Reports of complications caused by ERCP

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

Figures in parentheses denote mortality

Table 4. Mortality of acute cholangitis

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

[a] Only patients with shock
[b] Only severe cases
[c] Only AOSC

Table 5. Acute cholecystitis in patients with abdominal pain

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

Risk factors. Acute cholecystitis is the most frequent complication occurring in patients with cholelithiasis. According to the Comprehensive Survey of Living Conditions of the People on Health and Welfare conducted by the Medical Statistics Bureau of the Japanese Ministry of Health and Welfare, the number of those with acute cholecystitis has increased, from 3.9 million in 1979 to over 10 million in 1993 (Public Welfare Index in Japan; 1933; level 4).

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

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

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

AIDS as a risk factor. Enlarged liver and/or abnormal liver functions are observed in two/thirds of AIDS patients, some of whom have biliary tract disease. Biliary disease may occur by two mechanisms in AIDS patients: via AIDS cholangiopathy (which is more frequent) and via acute acalculous cholecystitis; AIDS patients with sclerosing cholangitis are also seen.

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

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

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

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

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

Review by Friedman[48]

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

Table 7. Etiological mechanisms of gallbladder diseases

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

Review by Michielsen et al.[53]

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

Ascaris as an etiologic factor. The complications of ascariasis include hepatic, biliary, and pancreatic diseases. Complications in the biliary tract include: (1) cholelithiasis with the ascarid as a nidus for stone formation, (2) acalculous cholecystitis (3), acute cholangitis (4), acute pancreatitis, and (5) hepatic abscess.[59] Biliary tract disease is caused by the obstruction of the hepatic and biliary tracts by the entry of ascarids from the duodenum through the papilla. Ascarids entering the biliary tract usually return to the duodenum in a week, but if they stay over 10 days there, they will die and form a nidus for stone formation.

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

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

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

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

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

Cholelithiasis is one of the main diseases associated with obesity. The Framingham study also confirms that cholelithiasis patients tend to be more obese than non-cholelithiasis patients (level 2a).[62] However, there is a report that this tendency is much more prominent in female than in male patients.[63] Not only obesity but also dieting is associated with the risk of cholelithiasis. Drastic dieting increases the risk of cholelithiasis in obese people (level 2b).[64–67] The incidences of both cholelithiasis and cholecystitis in obese people (age, 37–60 years; women with a body mass index [BMI] of 34 or higher and men with a BMI of 38 or more) are significantly higher that those in non-obese people (cholelithiasis, 5.8% vs 1.5%; Odds ratio [OR], 4.9; women 6.4% vs 22.6%; OR, 4.7; cholecystitis, 0.8% vs 3.4%; OR, 5.2; women 4.0% vs 11.2%; OR, 3.4) (level 2b).[68]

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

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

Pathophysiology

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

Pathological classification

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

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

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

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

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

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

Incidence of complications with advanced forms of acute cholecystitis

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

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

Prognosis

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

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

Recurrence rate of acute cholecystitis after conservative treatment

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

Table 8. Mortality of acute cholecystitis

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

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

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

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

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Diagnostic criteria and severity assessment of acute cholangitis: Tokyo Guidelines

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Abstract
Because acute cholangitis sometimes rapidly progresses to a severe form accompanied by organ dysfunction, caused by the systemic inflammatory response syndrome (SIRS) and/or sepsis, prompt diagnosis and severity assessment are necessary for appropriate management, including intensive care with organ support and urgent biliary drainage in addition to medical treatment. However, because there have been no standard criteria for the diagnosis and severity assessment of acute cholangitis, practical clinical guidelines have never been established. The aim of this part of the Tokyo Guidelines is to propose new criteria for the diagnosis and severity assessment of acute cholangitis based on a systematic review of the literature and the consensus of experts reached at the International Consensus Meeting held in Tokyo 2006. Acute cholangitis can be diagnosed if the clinical manifestations of Charcot's triad, i.e., fever and/or chills, abdominal pain (right upper quadrant or epigastric), and jaundice are present. When not all of the components of the triad are present, then a definite diagnosis can be made if laboratory data and imaging findings supporting the evidence of inflammation and biliary obstruction are obtained. The severity of acute cholangitis can be classified into three grades, mild (grade I), moderate (grade II), and severe (grade III), on the basis of two clinical factors, the onset of organ dysfunction and the response to the initial medical treatment. "Severe (grade III)" acute cholangitis is defined as acute cholangitis accompanied by at least one new-onset organ dysfunction. "Moderate (grade II)" acute cholangitis is defined as acute cholangitis that is unaccompanied by organ dysfunction, but that does not respond to the initial medical treatment, with the clinical manifestations and/or laboratory data not improved. "Mild (grade I)" acute cholangitis is defined as acute cholangitis that responds to the initial medical treatment, with the clinical findings improved.

Key words Cholangitis · Diagnosis · Severity of illness index · Guidelines

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Introduction

The pathogenesis of acute cholangitis is biliary infection associated with partial or complete obstruction of the biliary system caused by any of various etiologies including choledocholithiasis, benign and malignant strictures, biliary-enteric anastomotic malfunction, and indwelling biliary stent malfunction. Biliary infection alone does not cause clinical cholangitis unless biliary

obstruction raises the intraductal pressure in the bile duct to levels high enough to cause cholangiovenous or cholangiolymphatic reflux.[1] Thus, acute cholangitis progresses from local biliary infection to the systemic inflammatory response syndrome (SIRS), and advanced disease leads to sepsis with or without organ dysfunction.

Prior to the 1970s the mortality rate of patients with acute cholangitis was reported to be over 50%,[2,3] but advances in intensive care, new antibiotics, and biliary drainage dramatically reduced the mortality rate to less than 7% by the 1980s.[4,5] However, even in the 1990s the reported mortality rates in severe cases still ranged from 11% to 27%,[6–8] and even now the severe form of acute cholangitis remains a fatal disease unless appropriate management is instituted.

The clinical diagnosis of acute cholangitis is made on the basis of the clinical findings, such as Charcot's triad,[9] in combination with the laboratory data and imaging findings, and severity assessment is important because urgent biliary drainage is essential in "severe" cases. However, no standard criteria for the diagnostis and severity assessment of acute cholangitis have ever been established. In this portion of the Tokyo Guidelines, we propose diagnostic criteria and severity assessment criteria for acute cholangitis based on a review of the literature and the consensus of experts reached at the International Consensus Meeting for the Management of Acute Cholecystitis and Cholangitis, held on April 1–2, 2006, in Tokyo.

Diagnostic criteria for acute cholangitis

A variety of different names and definitions of acute cholangitis are found in the literature, depending on the authors.[6,8,10–17] Some authors defined acute cholangitis based on clinical sign's such as Charcot's triad (fever and/or chills, abdominal pain, and jaundice),[6,16–17] while others emphasized the presence of biliary obstruction or the properties of the bile (suppurative cholangitis),[10,13–14] as a result, there are no standard diagnostic criteria for acute cholangitis. The clinical information used to establish the diagnosis of acute cholangitis includes a history of biliary disease, symptoms and signs, laboratory data, and imaging findings.

Clinical context and manifestations

A history of biliary disease suggests a clinical diagnosis of cholangitis in patients who present with clinical manifestations such as fever, abdominal pain, and jaundice. Patients with a history of gallstone disease, previous biliary surgery, or the insertion of a biliary stent are more likely to develop biliary infection.

Clinical manifestations are an important factor in making the diagnosis of acute cholangitis. In 1877,[9] Charcot was the first to describe the clinical triad of fever, jaundice and abdominal pain as a clinical manifestation of acute cholangitis, and in 1959, Reynolds and Dragan[18] were the first to describe a severe form of cholangitis that included Charcot's triad plus septic shock and mental status change (Reynold's Pentad). Table 1 summarizes the incidence of each clinical manifestation reported in the literature.[6,8,10–17] Fever and abdominal pain are the most frequently observed clinical manifestations in acute cholangitis, with an incidence of each of up to 80% or more, whereas jaundice is observed in 60%–70% of cases. The incidence of Charcot's triad is reported in not more than 72% (range, 15.4% to 72%) of patients with acute cholangitis, and Reynolds' pentad is extremely rare, reported in only 3.5%–7.7% of the patients.

Laboratory data

Laboratory data indicative of inflammation (e.g., leukocytosis and an elevated C-reactive protein [CRP] level), and evidence of biliary stasis (e.g., hyperbilirubinemia, elevation of biliary enzymes and liver enzymes) are frequently seen in patients with acute cholangitis, and such laboratory findings support the diagnosis. Table 2 summarizes the positive rate for various blood tests in patients with acute cholangitis reported in the literature.[5,12,13,17,19–21]

Imaging findings

It is usually impossible to identify evidence of bile infection itself by imaging modalities. Imaging evidence of biliary dilatation (evidence of biliary obstruction) and/or the etiology of the underlying disease (tumor, gallstones, stent-related, etc.) can support the clinical diagnosis of cholangitis.

Diagnostic criteria for acute cholangitis

Table 3 shows the diagnostic criteria for acute cholangitis that were finally adopted by the Organizing Committee. The basic concepts of the criteria are as follows: (1) Charcot's triad is a definite diagnostic criterion for acute cholangitis, (2) if a patient does not have all the components of Charcot's triad (acute cholangitis is suspected), then definite diagnosis can be achieved if both an "inflammatory response" and "biliary obstruction" are demonstrated by the laboratory data (blood tests) and imaging findings.

Outcome of the Tokyo Consensus Meeting

More than 90% of the participants at the Tokyo Consensus Meeting agreed that the four criteria of: (1) a

Table 1. Incidence of clinical manifestation of acute cholangitis

Author	Disease	*n*	Charcot's triad (%)	Fever %	Jaundice %	Abdominal pain (%)	Reynold's pentad (%)	Shock %	Disturbed consciousness (%)
Csendes[10]	ASC	51 2	22	38.7	65.4	92.2		7	7.2
Thompson[11]	AC	66	About 60	100	66	59		7	9
Gigot[12]	AC	41 2	72				3.5	7.8	7
Boey[13]	AC	99	69.7	93.9	78.8	87.9	5.1	16.2	16.2
	SC	14					7	57	28
	NonSC	72					4	8	12
O'Connor[14]	AC	65	60				7.7	32	14
	SC	19	53				5	47	11
	NonSC	46	63				9	26	15
Lai[6]	Severe AC	86	56	66	93	90		64	
Haupert[15]	ASC	13	15.4	100	61.5	100	7.7	23.1	7.7
Welch[16]	ASC	5	50	80	60			0	20
	AOSC	15	50	88	67			33	27
Saharia[17]	AC	78		100	61.5	100		5.1	
Chijiiwa[8]	AOSC	27		63.0	70.3	96.3		25.9	22.2

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

Table 2. Positive rates for blood tests in acute cholangitis

Item	Positive rate (%)	No. of cases	Author
WBC >10000/mm^3	79	449	Gigot[12]
	63	78	Saharia[17]
	82	71	Boey[13]
Total bilirubin ↑	91	78	Saharia[17]
	78	74	Boey[13]
ALP ↑	93	449	Gigot JF[5]
	92	72	Saharia[17]
	74	74	Boey[13]
AST ↑	93	45	Saharia[17]
ALT ↑	97	35	Saharia[17]
AST or ALT ↑	57	74	Boey[13]
Prolonged prothrombin time	26	74	Boey[13]
Amylase ↑	7	74	Boey[13]
	35	54	Boey[13]
Creatinine ≧1.5 mg/d	16	125	Tai[5]
CA19-9 ↑	28	25	Ker[19]
	100	7	Albert[20]
Endotoxin ↑	36	11	Kanazawa[21]

WBC, white blood cells; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CA 19-9, carbohydrate antigen 19-9

Table 3. Diagnostic criteria for acute cholangitis

A. Clinical context and clinical manifestations	1. History of biliary disease 2. Fever and/or chills 3. Jaundice 4. Abdominal pain (RUQ or upper abdominal)
B. Laboratory data	5. Evidence of inflammatory response[a] 6. Abnormal liver function tests[b]
C. Imaging findings	7. Biliary dilatation, or evidence of an etiology (stricture, stone, stent etc)
Suspected diagnosis	Two or more items in A
Definite diagnosis	(1) Charcot's triad (2 + 3 + 4) (2) Two or more items in A + both items in B and item C

[a] Abnormal WBC count, increase of serum CRP level, and other changes indicating inflammation
[b] Increased serum ALP, r-GTP (GGT), AST, and ALT levels

history of biliary disease, (2) the clinical manifestations, (3) laboratory data indicative of the presence of inflammation and biliary obstruction, and (4) imaging findings indicative of biliary obstruction and/or evidence of etiology were suitable making the diagnosis of acute cholangitis.

Severity assessment of acute cholangitis

Patients with acute cholangitis may present with anything from a mild, self-limited illness to a severe, potentially life-threatening illness. Most cases respond to initial medical treatment consisting of general supportive therapy and intravenous antibiotics, but 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, requiring appropriate management that includes intensive care, organ-supportive care, and urgent biliary drainage, in addition to medical treatment.

Severity assessment criteria

Table 4 summarizes the risk factors reported in the literature for poor outcome in patients with acute cholangitis.[2,3,6,10,12,13,15,22–24] Organ dysfunction is the most common predictor of a poor outcome. On the other hand, based on the pathophysiology, "severe" acute cholangitis can also be defined as that which accompanies organ dysfunction caused by sepsis. Thus, "the onset of organ dysfunction" is an important factor in the definition of severe (grade III) acute cholangitis.

Another factor for the severity assessment of acute cholangitis is "response to initial medical treatment"; treatment consisting of general supportive care and antibiotics should be instituted as soon as possible for all patients who are diagnosed with acute cholangitis. Patients diagnosed with acute cholangitis that is not complicated by organ dysfunction, who did not respond to medical treatment and who continue to have SIRS and/or sepsis require additional treatment that includes either a change of antibiotic or biliary drainage. The severity of such cases is classified as moderate (grade II). Patients who respond to medical treatment and whose clinical manifestations and laboratory data improve are classified as having mild (grade I) disease. Table 5 and Table 6 show the concepts and criteria for the severity assessment of acute cholangitis.

Table 4. Prognostic factors in acute cholangitis

Prognostic factor	Positive value	References
Related to organ dysfunction		
Shock		2,10,13
Mental confusion		2,10
Elevated serum creatinine	>1.5–>2.0 mg/dl	3,10,12,22
Elevated BUN	>20–>64 mg/dl	10,12,24
Prolonged prothrombin time	>1.5–>2.0 s	10,23
Hyperbilirubinemia	>2.2–>10 mg/dl	2,5,6,10,13,22–24
Reduced platelet count	$<10 \times 10^4$–$<15 \times 10^4$/mm^3	3,6,24
Unrelated to organ dysfunction		
High fever	>39 °C–>40 °C	2,13
Leukocytosis	>20 000 /mm^3	2,3
Bacteremia		3,22
Endotoxemia		3
Hypoalbuminemia	<3.0 mg/dl	6,23,24
Liver abscess		12
Medical comorbidity		10,12,15,24
Elderly patient	>75 Years old	10,12,24
Malignancy as etiology		12,22

Table 5. Criteria for severity assessment of acute cholangitis

Criterion	Severity of acute cholangitis		
	Mild (grade I)	Moderate (grade II)	Severe (grade III)
Onset of organ dysfunction	No	No	Yes
Response to initial medical treatment[a]	Yes	No	No

[a] Consisting of general supportive care and antibiotics

Table 6. Definitions of severity assessment criteria for acute cholangitis

Mild (grade I) acute cholangitis		
"Mild (grade I)" acute cholangitis is defined as acute cholangitis which responds to the initial medical treatment[a]		
Moderate (grade II) acute cholangitis		
"Moderate (grade II)" acute cholangitis is defined as acute cholangitis that does not respond to the initial medical treatment[a] and is not accompanied by organ dysfunction		
Severe (grade III) acute cholangitis		
"Severe (grade III)" acute cholangitis is defined as acute cholangitis that is associated with the onset of dysfunction at least in any one of the following organs/systems:		
1. Cardiovascular system	Hypotension requiring dopamine ≧5 μg/kg per min, or any dose of dobutamine	
2. Nervous system	Disturbance of consciousness	
3. Respiratory system	PaO2/FiO2 ratio < 300	
4. Kidney	Serum creatinine > 2.0 mg/dl	
5. Liver	PT-INR > 1.5	
6. Hematological system	Platelet count < 100 000 /μl	

Note: compromised patients, e.g., elderly (>75 years old) and patients with medical comorbidities, should be monitored closely
[a] General supportive care and antibiotics

Outcome of the Tokyo Consensus Meeting

More than 70% of the participants at the Tokyo Consensus Meeting agreed that the severity of acute cholangitis should be divided into three grades — mild (grade I), moderate (grade II), and severe (grade III). To stratify acute cholangitis into the three grades, two different criteria were necessary, and it was decided to use "onset of organ dysfunction" and "response to the initial medical treatment" as criteria for the severity assessment of acute cholangitis (Table 5).

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Discussion at the Tokyo Consensus Meeting

Diagnostic criteria for acute cholangitis

"Acute cholangitis" is a clinical diagnosis. A definite diagnosis cannot be made on the basis of the results of any single test. The diagnosis of acute cholangitis is made on the basis of: (1) a history of biliary disease, (2) the clinical manifestations, (3) laboratory data that indicate the presence of inflammation and biliary obstruction, and (4) imaging findings that indicate biliary obstruction. More than 90% of participants at the International Consensus Meeting agreed that these four criteria were suitable for making the diagnosis of acute cholangitis (consensus was reached).

In terms of the clinical context and manifestations, a history of biliary disease and the clinical presentation are important factors in reaching the diagnosis. A history of biliary disease, such as gallstones, a history of previous biliary surgery, and having an indwelling biliary stent play an important role in making the diagnosis, as agreed upon by many participants at the Consensus Meeting. The more important clinical manifestations are clinical signs, such as Charcot's triad (fever and/or chills, abdominal pain, and jaundice). According to the literature, 50%–70% of acute cholangitis patients present with Charcot's triad, meaning that more than one-third of acute cholangitis patients do not present with all the components of Charcot's triad. The laboratory data and imaging findings can provide evidence to support the diagnosis in patients who have clinical manifestations of acute cholangitis but who do not show all the components of Charcot's triad (refer to Table 3).

Severity assessment criteria for acute cholangitis

A systematic review of the literature revealed that there were no standard criteria for either the diagnosis or severity assessment of acute cholangitis. Some authors have defined acute cholangitis associated with Reynold's pentad (Charcot's triad plus "shock" and "disturbance of consciousness") or organ dysfunction as "severe", while others have referred to it as "toxic cholangitis" or "acute obstructive suppurative cholangitis (AOSC)". A proposal that the onset of dysfunction of at least one organ be used as the criterion for severe (grade III) disease was supported by more than 90% of the panelists at the International Consensus Meeting (consensus was reached).

There was some argument about whether the score on an acute physiology scoring system, such as Acute physiology and chronic health evaluation (APACHE II) score or a multiple organ dysfunction scoring system, such as Marshall's system, or sepsis-related organ failure assessment (SOFA) system should be used as a criterion for severe (grade III) acute cholangitis. The principal advantage of these scoring systems is that they provide gradations of severity. The APACHE II system has been validated, especially for critical care patients, including patients with sepsis, and acute cholangitis can be interpreted as a subset of sepsis. The disadvantage of these scoring systems is that the scores are sometimes troublesome to calculate, and critically speaking, they have not been satisfactorily validated in patients with acute cholangitis. The vote on this argument showed that 37.8% of the panelists supported the use of APACHE II and 62.2% did not. As a result of this vote, the chairmen of this session, Drs. Yoshifumi Kawarada (Japan) and Henry Pitt (USA), proposed to remit the final decision on whether or not APACHE II should be included as a criterion for severe (grade III) acute cholangitis to the Organizing Committee, and this proposal was approved by the audience.

After the meeting, the Organizing Committee decided not to include the use of the APACHE II score as a criterion for the definition of severe (grade III) acute cholangitis, and we established the criteria by evaluating the presence or absence of the dysfunctions of six major organs/systems (refer to Table 6).

Deciding on the criteria for the assessment of acute cholangitis as moderate was the hardest part of this session. More than 70% of the participants agreed that a middle category of severity — moderate (grade II) — was necessary for acute cholangitis (consensus was reached).

The original definition of moderate (grade II) acute cholangitis was "acute cholangitis that requires biliary drainage but is not complicated by organ dysfunction." However, more than 80% of the participants voted against the need for biliary drainage as a criterion because it is a therapeutic intervention that should be selected only after the severity assessment has been completed. Thus, another criterion was needed in order

to stratify acute cholangitis into three grades. Other criteria for assessing acute cholangitis as moderate (grade II) were suggested by the audience. The most accepted criterion during the discussion was "resistance to initial treatment", with some others being "recurrence of symptoms" and "SIRS". The chairmen of this session also proposed to remit the final decision to the Organizing Committee, and this proposal was approved by the audience.

After the Meeting, the Organizing Committee concluded that the criterion for assorting into moderate (grade II) and mild (grade I) acute cholangitis should be "response to initial medical treatment consisting of general supportive care (intravenous fluid) and antibiotics," i.e., acute cholangitis that responds to medical treatment is defined as mild (grade I) acute cholangitis, whereas acute cholangitis that does not respond to the initial medical treatment but does not have organ dysfunction is defined as moderate (grade II) acute cholangitis (refer to Tables 5 and 6). No specific data or findings were adopted as criteria, because it is impossible to predict the need for biliary drainage based on the laboratory data or other findings. It was therefore concluded that we considered that it is important to stratify acute cholangitis as "severe" or "non-severe" at the time of diagnosis. Patients with the former require urgent biliary drainage in addition to general and organ-supportive treatment, while patients with the latter should be monitored to determine whether they respond to the initial medical treatment.

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Diagnostic criteria and severity assessment of acute cholecystitis: Tokyo Guidelines

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Abstract
The aim of this article is to propose new criteria for the diagnosis and severity assessment of acute cholecystitis, based on a systematic review of the literature and a consensus of experts. A working group reviewed articles with regard to the diagnosis and treatment of acute cholecystitis and extracted the best current available evidence. In addition to the evidence and face-to-face discussions, domestic consensus meetings were held by the experts in order to assess the results. A provisional outcome statement regarding the diagnostic criteria and criteria for severity assessment was discussed and finalized during an International Consensus Meeting held in Tokyo 2006. Patients exhibiting one of the local signs of inflammation, such as Murphy's sign, or a mass, pain or tenderness in the right upper quadrant, as well as one of the systemic signs of inflammation, such as fever, elevated white blood cell count, and elevated C-reactive protein level, are diagnosed as having acute cholecystitis. Patients in whom suspected clinical findings are confirmed by diagnostic imaging are also diagnosed with acute cholecystitis. The severity of acute cholecystitis is classified into three grades, mild (grade I), moderate (grade II), and severe (grade III). Grade I (mild acute cholecystitis) is defined as acute cholecystitis in a patient with no organ dysfunction and limited disease in the gallbladder, making cholecystectomy a low-risk procedure. Grade II (moderate acute cholecystitis) is associated with no organ dysfunction but there is extensive disease in the gallbladder, resulting in difficulty in safely performing a cholecystectomy. Grade II disease is usually characterized by an elevated white blood cell count; a palpable, tender mass in the right upper abdominal quadrant; disease duration of more than 72 h; and imaging studies indicating significant inflammatory changes in the gallbladder. Grade III (severe acute cholecystitis) is defined as acute cholecystitis with organ dysfunction.

Key words Acute cholecystitis · Diagnosis · Severity of illness index · Guidelines · Infection

Introduction

Early diagnosis of acute cholecystitis allows prompt treatment and reduces both mortality and morbidity.

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The accurate diagnosis of typical as well as atypical cases of acute cholecystitis requires specific diagnostic criteria. Acute cholecystitis has a better prognosis than acute cholangitis, but may require immediate management, especially in patients with torsion of the gallbladder and emphysematous, gangrenous, or suppurative cholecystitis. The lack of standard criteria for diagnosis and severity assessment is reflected by the wide range of reported mortality rates in the literature, and this lack makes it impossible to provide standardized optimal treatment guidelines for patients. In these Guidelines we propose specific criteria for the diagnosis and severity assessment of acute cholecystitis, based on the best available evidence and the experts' consensus achieved at the International Consensus Meeting for the Management of Acute Cholecystitis and Cholangitis, held on April 1–2, 2006, in Tokyo.

Diagnostic criteria for acute cholecystitis

Diagnosis is the starting point of the management of acute cholecystitis, and prompt and timely diagnosis should lead to early treatment and lower mortality and morbidity. Specific diagnostic criteria are necessary to accurately diagnose typical, as well as atypical cases. The Guidelines propose diagnostic criteria for acute cholecystitis (Table 1). C-reactive protein (CRP) is not commonly measured in many countries. However, because acute cholecystitis is usually associatied with an elevation of CRP level by 3 mg/dl or more, CRP was included. Diagnosis of acute cholecystitis by elevation of CRP level (3 mg/dl or more), with ultrasonographic findings suggesting acute cholecystitis, has a sensitivity of 97%, specificity of 76%, and positive predictive value of 95% (level 1b).[1] After the discussion during the Tokyo International Consensus Meeting, almost unanimous agreement was achieved on the criteria (Table 2). However, 19% of the panelists from abroad expressed the necessity for minor modifications, because, in the provisional version, the diagnostic criteria did not include technetium hepatobiliery iminodiacetic acid (Tc-HIDA) scan as an item.

Table 1. Diagnostic criteria for acute cholecystitis

A. Local signs of inflammation etc.:
   (1) Murphy's sign, (2) RUQ mass/pain/tenderness
B. Systemic signs of inflammation etc.:
   (1) Fever, (2) elevated CRP, (3) elevated WBC count
C. Imaging findings: imaging findings characteristic of acute cholecystitis

Definite diagnosis
(1) One item in A and one item in B are positive
(2) C confirms the diagnosis when acute cholecystitis is suspected clinically

Note: acute hepatitis, other acute abdominal diseases, and chronic cholecystitis should be excluded

Imaging findings of acute cholecystitis

Ultrasonography findings (level 4)[2–5]

Sonographic Murphy sign (tenderness elicited by pressing the gallbladder with the ultrasound probe)
Thickened gallbladder wall (>4 mm; if the patient does not have chronic liver disease and/or ascites or right heart failure)
Enlarged gallbladder (long axis diameter >8 cm, short axis diameter >4 cm)
Incarcerated gallstone, debris echo, pericholecystic fluid collection
Sonolucent layer in the gallbladder wall, striated intramural lucencies, and Doppler signals.

Magnetic resonance imaging (MRI) findings (level 1b-4)[6–9]

Pericholecystic high signal
Enlarged gallbladder
Thickened gallbladder wall.

Computed tomography (CT) findings (level 3b)[10]

Thickened gallbladder wall
Pericholecystic fluid collection
Enlarged gallbladder
Linear high-density areas in the pericholecystic fat tissue.

Table 2. Answer pad responses on the diagnostic criteria for acute cholecystitis

	Agree	Agree, but needs minor modifications	Disagree
Total (n = 110)	92%	8%	0%
Panelists from abroad (n = 21)	81%	19%	0%
Japanese panelists (n = 20)	100%	0%	0%
Audience (n = 69)	93%	7%	0%

Tc-HIDA scans (level 4)[11,12]

Non-visualized gallbladder with normal uptake and excretion of radioactivity

Rim sign (augmentation of radioactivity around the gallbladder fossa).

Severity assessment criteria of acute cholecystitis

Concept of severity grading of acute cholecystitis

Patients with acute cholecystitis may present with a spectrum of disease stages ranging from a mild, self-limited illness to a fulminant, potentially life-threatening illness. In these Guidelines we classify the severity of acute cholecystitis into the following three categories: "mild (grade I)", "moderate (grade II)", and "severe (grade III)". A category for the most severe grade of acute cholecystitis is needed because this grade requires intensive care and urgent treatment (operation and/or drainage) to save the patient's life. However, the vast majority of patients present with less severe forms of the disease. In these patients, the major practical question regarding management is whether it is advisable to perform cholecystectomy at the time of presentation in the acute phase or whether other strategies of management should be chosen during the acute phase, followed by an interval cholecystectomy. Therefore, to guide the clinician, the severity grading includes a "moderate" group based on criteria predicting when conditions might be unfavorable for cholecystectomy in the acute phase (level 2b-4).[13–18] Patients who fall neither into the severe nor the moderate group form the majority of patients with this disease; their disease is suitable for management by cholecystectomy in the acute phase, if comorbidities are not a factor. Definitions of the three grades are given below.

Mild (grade I) acute cholecystitis

Mild acute cholecystitis occurs in a patient in whom there are no findings of organ dysfunction, and there is mild disease in the gallbladder, allowing for cholecystectomy to be performed as a safe and low-risk procedure. These patients do not have a severity index that meets the criteria for "moderate (grade II)" or "severe (grade III)" acute cholecystitis.

Moderate (grade II) acute cholecystitis

In moderate acute cholecystitis, the degree of acute inflammation is likely to be associated with increased operative difficulty to perform a cholecystectomy (level 2b-4).[13–18]

Severe (grade III) acute cholecystitis

Severe acute cholecystitis is associated with organ dysfunction.

Criteria for the severity assessment of acute cholecystitis

Acute cholecystitis has a better outcome/prognosis than acute cholangitis but requires prompt treatment if 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 the 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, are sometimes used to evaluate organ dysfunction in critically ill patients. The Guidelines classify the severity of acute cholecystitis into three grades (Tables 3–5): "severe (grade III)": acute cholecystitis associated with organ dysfunction, "moderate (grade II)": acute cholecystitis associated with difficulty to perform cholecystectomy due to local inflammation, and "mild (grade I)": acute cholecystitis which does not meet the criteria of "severe" or "moderate" acute cholecystitis (these patients have acute cholecystitis but no

Table 3. Criteria for mild (grade I) acute cholecystitis

"Mild (grade I)" acute cholecystitis does not meet the criteria of "severe (grade III)" or "moderate (grade II)" acute cholecystitis. Grade I can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and only mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.

Table 4. Criteria for moderate (grade II) acute cholecystitis

"Moderate" acute cholecystitis is accompanied by any one of the following conditions:

1. Elevated WBC count (>18000/mm^3)
2. Palpable tender mass in the right upper abdominal quadrant
3. Duration of complaints >72 h[a]
4. Marked local inflammation (biliary peritonitis, pericholecystic abscess, hepatic abscess, gangrenous cholecystitis, emphysematous cholecystitis)

[a] Laparoscopic surgery in acute cholecystitis should be performed within 96 h after the onset (level 2b-4)[13,14,16]

Table 5. Criteria for severe (grade III) acute cholecystitis

"Severe" acute cholecystitis is accompanied by dysfunctions in any one of the following organs/systems

1. Cardiovascular dysfunction (hypotension requiring treatment with dopamine ≧5 μg/kg per min, or any dose of dobutamine)
2. Neurological dysfunction (decreased level of consciousness)
3. Respiratory dysfunction (PaO_2/FiO_2 ratio <300)
4. Renal dysfunction (oliguria, creatinine >2.0 mg/dl)
5. Hepatic dysfunction (PT-INR >1.5)
6. Hematological dysfunction (platelet count <100000/mm^3)

Table 6. Answer pad responses on the criteria for severe (grade III) acute cholecystitis

	Agree	Agree, but needs minor modifications	Disagree
Total (n = 110)	90%	10%	0%
Panelists from abroad (n = 21)	95%	5%	0%
Japanese panelists (n = 21)	81%	19%	0%
Audience (n = 68)	91%	9%	0%

Table 7. Answer pad responses on the criteria for moderate (grade II) acute cholecystitis

	Agree	Agree, but needs minor modifications	Disagree
Total (n = 109)	78%	22%	0%
Panelists from abroad (n = 22)	77%	23%	0%
Japanese panelists (n = 22)	91%	9%	0%
Audience (n = 65)	74%	26%	0%

organ dysfunction, and there are mild inflammatory changes in the gallbladder, so that a cholecystectomy can be performed with a low operative risk). Almost unanimous agreement on the criteria was achieved (Tables 6 and 7). When acute cholecystitis is accompanied by acute cholangitis, the criteria for the severity assessment of acute cholangitis should also be taken into account. Being "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.

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Discussion at the Tokyo International Consensus Meeting

Diagnostic criteria for acute cholecystitis

The clinical diagnosis of acute cholecystitis is traditionally based on the patient's clinical presentation, and it is confirmed by the imaging findings. Hence, the initial provisional diagnostic criteria for acute cholecystitis comprised: (1) clinical signs and symptoms, (2) laboratory data, and (3) imaging findings. In the discussion on criteria for "clinical signs and symptoms", 92% of the Japanese panelists agreed, whereas only 65% of the panelists from abroad agreed and 4% disagreed. In regard to the criteria for "laboratory data", 20% of the Japanese panelists and 39% of the panelists from abroad voted "agree, but needs minor modifications". After a discussion among the panelists, several changes were made. In regard to the proposed criteria for "imaging findings", 66%–71% of the Japanese panelists agreed and about 30% of the panelists voted "agree, but needs minor modifications", and 4% of the panelists from abroad disagreed, because Tc-HIDA scans were not included. Discussion at the International Consensus Meeting led to the reorganization of these categories as: (1) local signs of inflammation, (2) systemic signs of inflammation, and (3) imaging findings. "Suspected diagnosis" in the provisional criteria was deleted, and two conditions for "definite diagnosis" were established in the final diagnostic criteria. After the discussion, 100% of the Japanese panelists and 81% of the panelists from abroad agreed on the final version (refer to Tables 1 and 2; consensus was reached).

Severity assessment criteria for acute cholecystitis

Concerning criteria for severe (grade III) acute cholecystitis, 81% of the Japanese panelists and 95% of the panelists from abroad agreed with the criteria (refer to Tables 5 and 6; consensus was reached). The acute physiology and chronic health evaluation II (APACHE II) score was not included in the assessment criteria, because it is too complicated to apply in community hospitals.

The criteria for moderate (grade II) acute cholecystitis can be defined as acute cholecystitis associated with local inflammatory conditions that make cholecystectomy difficult (Steven Strasberg, USA; Dirk J. Gouma, the Netherlands; Henry Pitt, USA; Sheung-Tat Fan and Joseph W.Y. Lau, Hong Kong; Serafin C. Hilvano, Philippines). On the basis of these aspects, the final criteria for moderate (grade II) acute cholecystitis were defined and were agreed on by 91% of the Japanese panelists and 77% of those from abroad (refer to Tables 4 and 7; consensus was reached).

The criteria for mild (grade I) acute cholecystitis were agreed on by approximately 90% of both the Japanese panelists and the panelists from abroad (consensus was reached).

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Flowcharts for the diagnosis and treatment of acute cholangitis and cholecystitis: Tokyo Guidelines

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Abstract
Diagnostic and therapeutic strategies for acute biliary inflammation/infection (acute cholangitis and acute cholecystitis), according to severity grade, have not yet been established in the world. Therefore we formulated flowcharts for the management of acute biliary inflammation/infection in accordance with severity grade. For mild (grade I) acute cholangitis, medical treatment may be sufficient/appropriate. For moderate (grade II) acute cholangitis, early biliary drainage should be performed. For severe (grade III) acute cholangitis, appropriate organ support such as ventilatory/circulatory management is required. After hemodynamic stabilization is achieved, urgent endoscopic or percutaneous transhepatic biliary drainage should be performed. For patients with acute cholangitis of any grade of severity, treatment for the underlying etiology, including endoscopic, percutaneous, or surgical treatment should be performed after the patient's general condition has improved. For patients with mild (grade I) cholecystitis, early laparoscopic cholecystectomy is the preferred treatment. For patients with moderate (grade II) acute cholecystitis, early laparoscopic or open cholecystectomy is preferred. In patients with extensive local inflammation, elective cholecystectomy is recommended after initial management with percutaneous gallbladder drainage and/or cholecystostomy. For the patient with severe (grade III) acute cholecystitis, multiorgan support is a critical part of management. Biliary peritonitis due to perforation of the gallbladder is an indication for urgent cholecystectomy and/or drainage. Delayed elective cholecystectomy may be performed after initial treatment with gallbladder drainage and improvement of the patient's general medical condition.

Key words Cholangitis · Acute cholecystitis · Cholecystectomy · Laparoscopic cholecystectomy · Biliary · Drainage · Guidelines

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Introduction

Acute biliary inflammation/infection is classified as either acute cholangitis or acute cholecystitis, and ranges from mild forms that improve with medical treatment to severe forms that require intensive care and urgent intervention. The medical condition of a patient with biliary inflammation/infection is likely to deteriorate rapidly and the condition can become life-threatening. Early diagnosis should be made based on clinical signs/symptoms and laboratory findings. The type and timing of treatment should be based on the grade of severity of the disease.

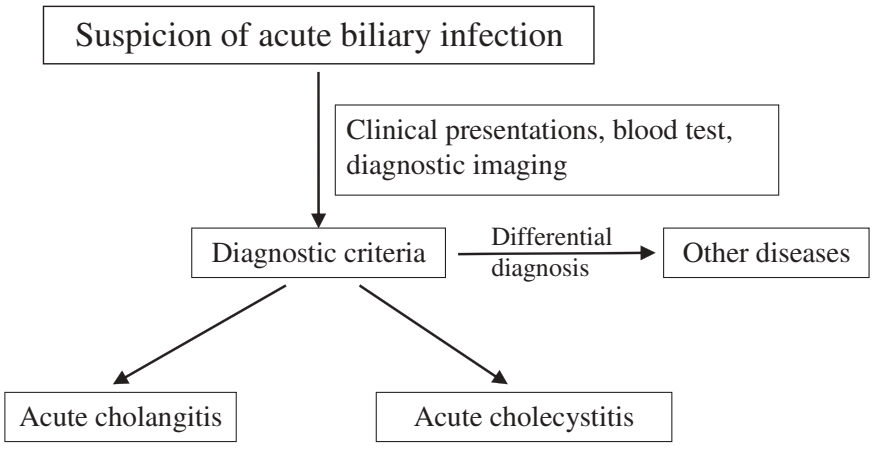

Fig. 1. Flowchart showing general guidance for the management of acute biliary infection

Although endoscopic and laparoscopic techniques have advanced recently (level 1b–2b),[1,2] the treatment of severe acute biliary inflammation/infection still results in fatalities and increased hospital costs. To our knowledge, there are no definite diagnostic and therapeutic guidelines for acute biliary inflammation/infection according to the grade of severity of the disease. This article describes the management strategy for biliary inflammation/infection in accordance with the severity of the biliary disease. Guidelines were developed, based on best clinical evidence and discussions at the International Consensus Meeting held in Tokyo on April 1–2, 2006.

General guidance for the management of acute biliary inflammation/infection

A flowchart showing general guidance for the management of acute biliary inflammation/infection is presented in Fig. 1.

Clinical presentation

Clinical findings associated with acute cholangitis include abdominal pain, jaundice, fever (Charcot's triad), and rigor. The triad was already reported as an indicator of hepatic fever by Charcot in 1877,[3] and has been, historically, used as the generally accepted clinical findings of acute cholangitis. About 50%–70% of patients with acute cholangitis develop all three symptoms (level 2b–4).[4–7] Reynolds' pentad (Charcot's triad plus shock and a decreased level of consciousness) was presented in 1959, when Reynolds and Dargan[8] defined acute obstructive cholangitis. The pentad is often used to indicate severe (grade III) cholangitis, but shock and a decreased level of consciousness are observed in only 30% or fewer patients with acute cholangitis (level 2b–4).[4–7] A history of biliary disease, such as gallstones, previous biliary procedures, or the placement of a biliary stent are factors that are very helpful to suggest a diagnosis of acute cholangitis.

Clinical symptoms of acute cholecystitis include abdominal pain (right upper abdominal pain), nausea, vomiting, and fever (level 2b–4).[9–11] 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 has a specificity of 79%–96% (level 2b–3b)[9,11] for acute cholecystitis.

Blood tests

The diagnosis of acute cholangitis requires a white blood cell count; measurement of the C-reactive protein level; and liver function tests, including alkaline phosphatase, gamma-glutamyltranspeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin. Assessment of the severity of the illness requires knowledge of the platelet count, blood urea nitrogen, creatinine, and prothrombin time (PT). Blood cultures are also helpful for severity assessment, as well as for the selection of antimicrobial drugs. Hyperamylasemia is a useful parameter to identify complications such as choledocholithiasis causing biliary pancreatitis (level 1a).[12]

There is no specific blood test for acute cholecystitis; however, the white blood cell count and the measurement of C-reactive protein is very useful in confirming an inflammatory process. Bilirubin, blood urea nitrogen, creatinine, and PT are very useful in assessing the disease severity status of the patient.

Diagnostic imaging

Abdominal ultrasound (US) and abdominal computerized tomography (CT) with intravenous contrast are very helpful studies in evaluating patients with acute

biliary tract disease. Abdominal US should be performed in all patients suspected of having acute biliary inflammation/infection. Ultrasound examination has satisfactory diagnostic capability when it is performed not only by specialists but also by emergency physicians (level 1b).[13,14]

The role of diagnostic imaging in acute cholangitis is to determine the presence/absence of biliary obstruction, the level of the obstruction, and the cause of the obstruction, such as gallstones and/or biliary strictures. Assessment should include both US and CT. These studies complement each other and CT may better demonstrate dilatation of the bile duct and pneumobilia.

Some of the characteristic finding of acute cholecystitis include an enlarged gallbladder, thickened gallbladder wall, gallbladder stones and/or debris in the gallbladder, sonographic Murphy's sign, pericholecystic fluid, and pericholecystic abscess. Sonographic Murphy's sign is a very reliable finding of acute cholecystitis, with a specificity exceeding 90% (level 3b,4).[15,16] CT scan or even plain X-ray may demonstrate free air, pneumobilia, and ileus.

Differential diagnosis

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

Flowchart for the management of acute cholangitis

A flowchart for the management of acute cholangitis is shown in Fig. 2. The treatment of acute cholangitis should be guided by the grade of severity of the disease. Biliary drainage and antibiotics are the two most important elements of treatment. When a diagnosis of acute cholangitis is suspected, medical treatment, including nil per os (NPO) and the use of intravenous fluids, antibiotics, and analgesia, together with close monitoring of blood pressure, pulse, and urinary output should be initiated. Simultaneously, a severity assessment of the cholangitis should be documented, even if it is mild. Frequent reassessment is important, and patients may need to be reclassified as having mild (grade I), moderate (grade II), or severe (grade III) disease, based on the response to medical treatment. Appropriate treatment should be performed in accordance with the severity grade. Patients with concomitant diseases such as acute pancreatitis or malignant tumor, and elderly patients are likely to progress to a severe level; therefore, such patients should be monitored frequently.

Mild (grade I) acute cholangitis

Medical treatment may be sufficient. Biliary drainage is not required in most cases. However, for non-responders to medical treatment, the necessity of biliary

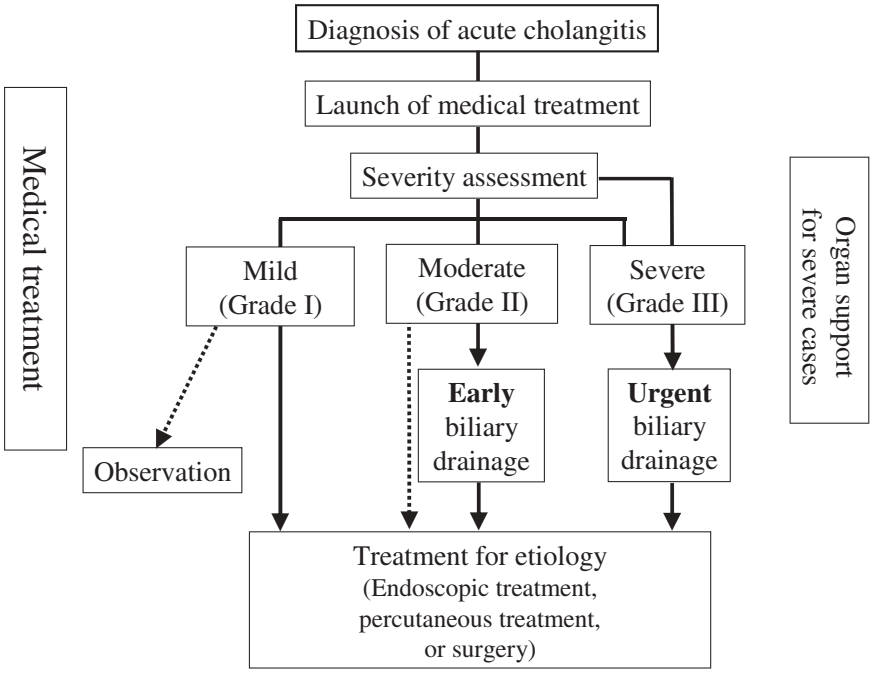

Fig. 2. Flowchart for the management of acute cholangitis

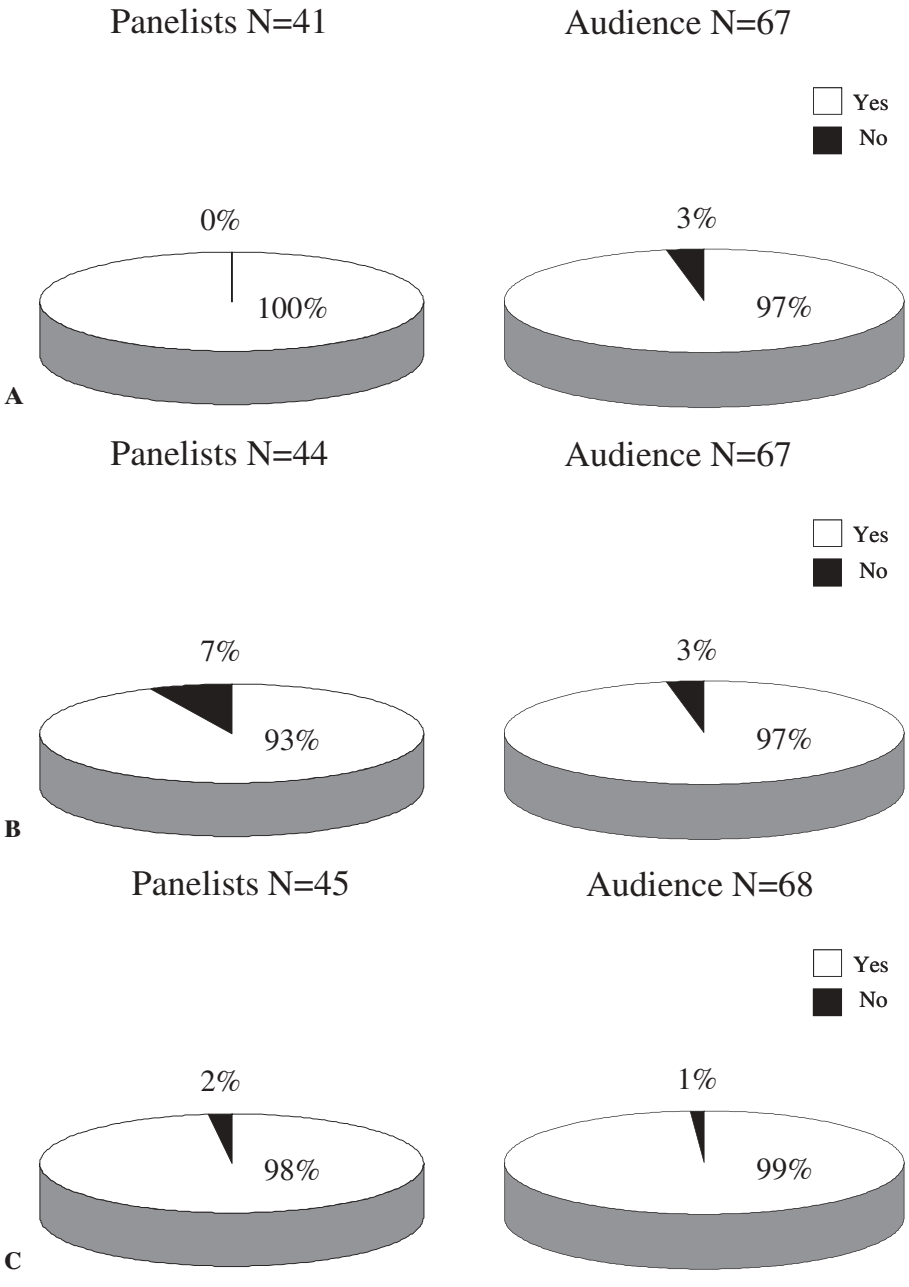

Fig. 3. **A** Responses to the question "Do you agree with the flowchart for the management of mild acute (grade I) cholangitis?" The flowchart for the management of mild acute (grade I) cholangitis was agreed upon by 100% and 97% of the panelists and the audience, respectively. **B** Responses to the question "Do you agree with the flowchart for the management of moderate acute (grade II) cholangitis?" The flowchart for the management of moderate acute (grade II) cholangitis was agreed upon by 93% and 97% of the panelists and the audience, respectively. **C** Responses to the question "Do you agree with the flowchart for the management of severe acute (grade III) cholangitis?" The flowchart for the management of severe acute (grade III) cholangitis was agreed upon by 98% and 99% of the panelists and the audience, respectively

drainage should be considered. Treatment options such as endoscopic, percutaneous, or operative intervention may be required, depending on the etiology. Some patients, such as those who develop postoperative cholangitis, may only require antibiotics and generally do not require intervention.

Moderate (grade II) acute cholangitis

Patients with acute cholangitis who do not respond to medical treatment have moderate (grade II) acute cholangitis. In these patients, early endoscopic or percutaneous drainage or even emergent operative drainage with a T-tube should be performed. A definitive procedure should be performed to remove the cause of the obstruction once the patient is in a stable condition.

Severe (grade III) acute cholangitis

Patients with acute cholangitis and organ failure are classified as having severe (grade III) acute cholangitis. These patients require organ support, such as ventilatory/circulatory management (e.g., endotracheal intubation, artificial respiration management, and the use of vasopressin), and treatment for disseminated

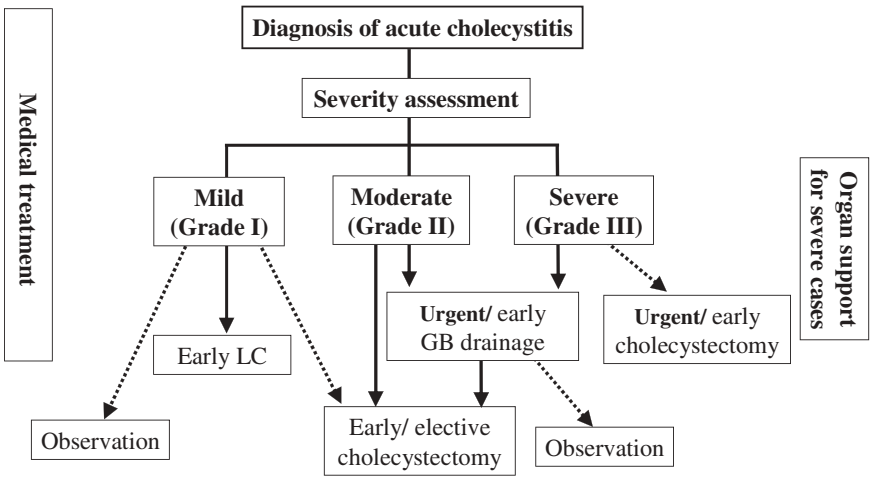

Fig. 4. Flowchart for the management of acute cholecystitis. *GB*, gallbladder; *LC*, laparoscopic cholecystectomy

intravascular coagulation (DIC) in addition to the general medical management. Urgent biliary drainage must be anticipated. When the patient is stabilized, urgent (ASAP) endoscopic or percutaneous transhepatic biliary drainage or an emergent operation with decompression of the bile duct with a T-tube should be performed. Definitive treatment of the cause of the obstruction, including endoscopic, percutaneous, or operative intervention, should be considered once the acute illness has resolved.

Results of the Tokyo International Consensus Meeting

At the International Consensus Meeting, responses to the flowcharts for the management of the different grades of acute cholangitis were elicited and a consensus was reached (Fig. 3).

Flowchart for the management of acute cholecystitis

A flowchart for the management of acute cholecystitis is shown in Fig. 4. Early cholecystectomy is recommended for most patients, with laparoscopic cholecystectomy as the preferred method. Among high-risk patients, percutaneous gallbladder drainage is an alternative therapy for those patients who cannot safely undergo urgent/early cholecystectomy (level 4).[17,18]

When a diagnosis of acute cholecystitis is suspected, medical treatment, including NPO, intravenous fluids, antibiotics, and analgesia, together with close monitoring of blood pressure, pulse, and urinary output should be initiated. Simultaneously, the grade of severity needs to be established. Appropriate treatment should be performed in accordance with the severity grade. The assessment of operative risk should also be evaluated based on the severity grade.

After the acute inflammation has been resolved by medical treatment and gallbladder drainage, it is desirable to perform a cholecystectomy to prevent recurrence. In surgically high-risk patients with cholecystolithasis, medical support after percutaneous cholecystolithotomy should be considered (level 4).[19–21] For patients with acalculous cholecystitis, cholecystectomy is not required, because recurrence of acute acalculous cholecystitis after gallbladder drainage is rare (level 4).[17,22]

Mild (grade I) acute cholecystitis

Early laparoscopic cholecystectomy is the preferred treatment. Elective cholecystectomy may be selected (if early cholecystectomy is not performed) in order to improve other medical problems.

Moderate (grade II) acute cholecystitis

Early laparoscopic or open cholecystectomy is preferred. If a patient has serious local inflammation making early cholecystectomy difficult, then percutaneous or operative drainage of the gallbladder is recommended. Elective cholecystectomy can be performed after improvement of the acute inflammatory process.

Severe (grade III) acute cholecystitis

Severe (grade III) acute cholecystitis is accompanied by organ dysfunction and/or severe local inflammation. Appropriate organ support in addition to medical treatment is necessary for patients with organ dysfunction. Management of severe local inflammation by percutaneous gallbladder drainage and/or cholecystectomy is needed. Biliary peritonitis due to perforation of the gallbladder is an indication for urgent cholecystectomy

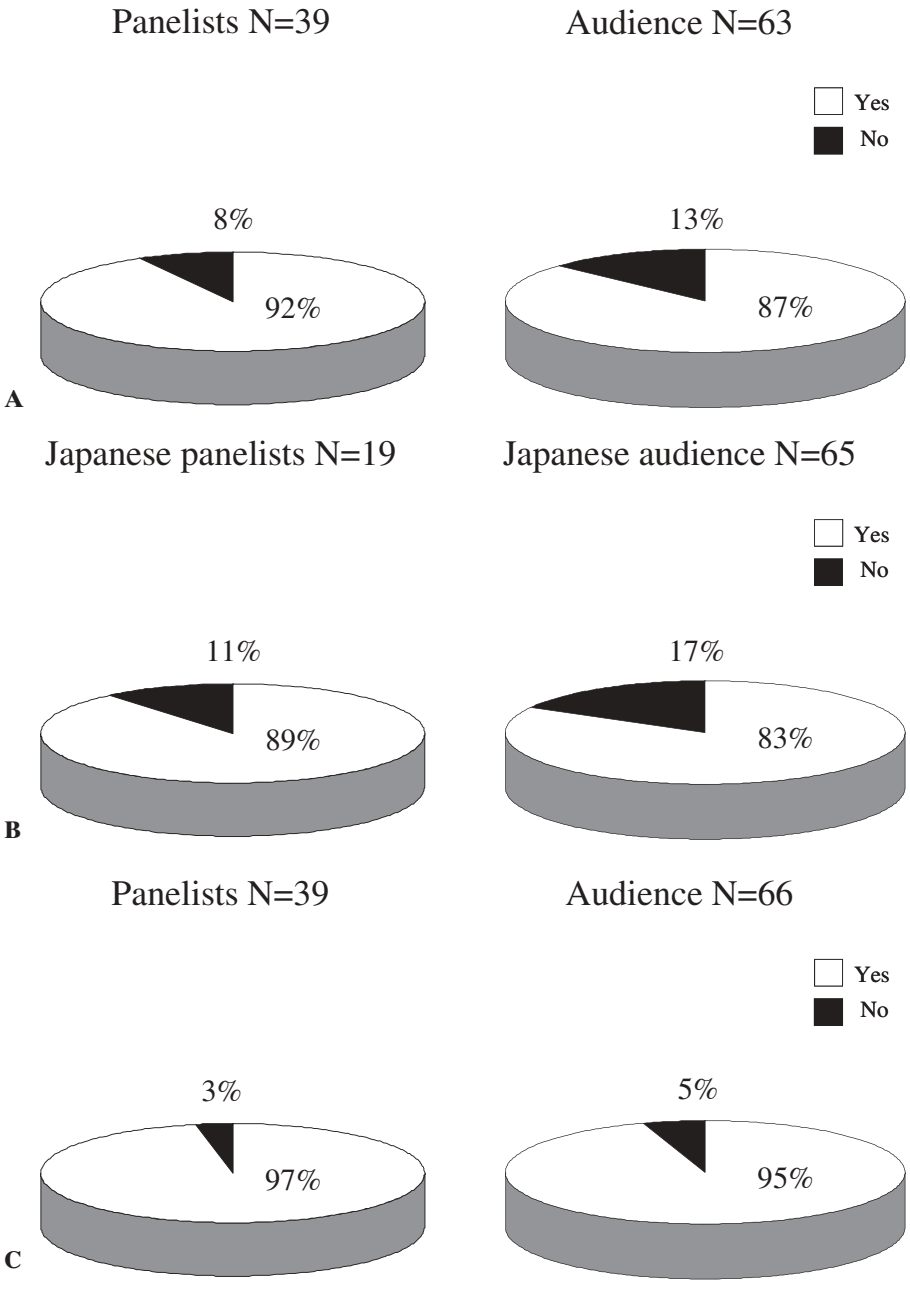

Fig. 5. A Responses to the question "Do you agree with the flowchart for the management of mild acute (grade I) cholecystitis?" The flowchart for the management of mild acute (grade I) cholecystitis was agreed upon by 92% and 87% of the panelists and the audience, respectively. **B** Responses to the question "Do you agree with the flowchart for the management of moderate acute (grade II) cholecystitis?" The flowchart for the management of moderate acute (grade II) cholecystitis was agreed upon by 89% and 83% of the Japanese panelists and the Japanese audience, respectively. **C** Responses to the question "Do you agree with the flowchart for the management of severe acute (grade III) cholecystitis?" The flowchart for the management of severe acute (grade III) cholecystitis was agreed upon by 97% and 95% of the panelists and audience, respectively

and drainage. Elective cholecystectomy may be performed after improvement of the acute illness by gallbladder drainage.

Results of the Tokyo International Consensus Meeting

At the International Consensus Meeting, flowcharts for the management of mild (grade I) and severe (grade III) acute cholecystitis were agreed upon by almost all of the participants; however, the flowchart for moderate (grade II) acute cholecystitis was agreed upon by fewer than 90% of the participants (Fig. 5).

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Discussion at the Tokyo International Consensus Meeting

General guidance

Acute biliary inflammation/infection consists of acute cholangitis and acute cholecystitis. In these infectious diseases, bacterial contamination is an essential condition, but inflammation has a wider meaning and includes not only infection but also other inflammation caused by non-bacterial vectors (Sun-Whe Kim, Korea). It may be difficult to initially determine whether the inflammation is progressing to an bacterial infection (Thomas R. Gadacz, USA); therefore, in this article, we adopted the term "acute biliary inflammation/infection".

As for general guidance for the management of acute biliary inflammation/infection, most aspects were accepted with great concordance. During the initial evaluation of a patient, information on a past history of biliary disease (gallstone, previous biliary surgery, and biliary stent placement) was emphasized (Jacques Belghiti, France; Philippus C. Bornman, South Africa; and Steven M. Strasberg, USA). Jacques Belghiti added that septicemia arising from other diseases needs to be differentiated from acute cholangitis.

Flowchart for the management of acute cholangitis

Concerning the treatment of acute cholangitis, the particular importance of antibiotics as well as urgent biliary drainage was confirmed (Jacques Belghiti; Joseph W.Y. Lau, Hong Kong, and Steven M. Strasberg). There were few controversial matters in the flowchart for the management of acute cholangitis. Joseph W.Y. Lau advocated that mild cholangitis and moderate cholangitis should be combined, because many patients with moderate cholangitis would easily revert to the mild grade within 12 h after successful medical treatment, and he suggested that severity assessment should depend on whether patients responded to the initial treatment. This statement implies that severity assessment should be

repeated after the initiation of treatment for acute cholangitis.

Flowchart for the management of acute cholecystitis

There were several controversies over the treatment of acute cholecystitis. Early cholecystectomy is indicated for most patients with acute cholecystitis, and laparoscopic cholecystectomy is preferred for experienced surgeons. Several randomized controlled trials comparing early and delayed operation conducted in the 1970s to 1980s found that early surgery had the advantages of less blood loss, shorter operation time, a lower complication rate, and a shorter hospital stay. Some Japanese doctors advocated that early cholecystectomy should not be recommended because early cholecystectomy was not prevalent in Japan. Steven M. Strasberg mentioned: "We have to be willing to accept the fact that we may need to change our practice based upon the evidence". Results of randomized controlled trials comparing early laparoscopic cholecystectomy with delayed laparoscopic cholecystectomy have also shown that early laparoscopic surgery is superior to delayed surgery in terms of the conversion rate to open surgery, complication rate, and total hospital stay. Toshihiko Mayumi (Japan) mentioned that because laparoscopic cholecystectomy by inexperienced surgeons resulted in more frequent intraoperative complications than open cholecystectomy, the laparoscopic procedure should not be overemphasized.

There was more discussion to determine the treatment strategy for acute moderate (grade II) cholecystitis. Before the start of the international symposium it was considered that urgent/early cholecystectomy should be performed for these patients. Steven M. Strasberg mentioned: "For patients with acute moderate cholecystitis (patients who have a white [cell] count over 18000; patients who have cholecystitis for more than 72 h; patients who have a palpable inflammatory mass), early cholecystectomy is going to be maybe very difficult. Therefore do we really want to say to the general surgeon in a small hospital that we recommend that when the white [cell] count is over 18000 that he takes the patient to the operating room? I do not think so." After the statement of his opinion, delayed elective cholecystectomy was recommended for acute moderate (grade II) cholecystitis with severe local inflammation. On the other hand, Eduardo de Santibanes (Argentina) advocated that early laparoscopic cholecystectomy could be performed for patients with acute moderate cholecystitis.

The treatment courses for mild (grade I) and severe (grade III) cholecystitis were accepted without major adverse opinions. The recommendation of early laparoscopic cholecystectomy for mild (grade I) cases and gallbladder drainage for severe (grade III) cases obtained consensus. Some Japanese doctors suggested that endoscopic gallbladder drainage as well as percutaneous gallbladder drainage should be recommended. However, Jacques Belghiti rejected this suggestion, because there was poor evidence for efficacy, and because endoscopic gallbladder drainage needed a special technique. Thomas R. Gadacz added surgical cholecystostomy to one of the methods for gallbladder drainage.

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Antimicrobial therapy for acute cholangitis: Tokyo Guidelines

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Abstract
Antimicrobial agents should be administered to all patients with suspected acute cholangitis as a priority as soon as possible. Bile cultures should be performed at the earliest opportunity. The important factors which should be considered in selecting antimicrobial therapy include the agent's activity against potentially infecting bacteria, the severity of the cholangitis, the presence or absence of renal and hepatic diseases, the patient's recent history of antimicrobial therapy, and any recent culture results, if available. Biliary penetration of the microbial agents should also be considered in the selection of antimicrobials, but activity against the infecting isolates is of greatest importance. If the causative organisms are identified, empirically chosen antimicrobial drugs should be replaced by narrower-spectrum antimicrobial agents, the most appropriate for the species and the site of the infection.

Key words Cholangitis · Anti-infective agents · Guidelines · Infection · Biliary

Introduction

In the medical treatment, of acute cholangitis, antimicrobial agents should be chosen empirically and carefully. As soon as a diagnosis of acute cholangitis is considered, antimicrobial agents should be selected empirically, with careful consideration of several factors, including antimicrobial activity against the causative bacteria, the severity of the cholangitis, the presence/absence of renal and hepatic disease, a recent (1-year) history of antimicrobial therapy, local susceptibility patterns (antibiogram), and (although controversies still exist) the biliary penetration of the antimicrobial agents. Whenever any presumptive or empirical antimicrobial agents are used, they should be switched for the best available narrower-spectrum agents to avoid superinfection or the emergence of antimicrobial resistance as a cause of treatment failure. Long-term administration without an acceptable rationale should be avoided. In this article, we review previous bacteriological studies and clinical trials. We also provide current recommendations for the antimicrobial agents to be used for acute cholangitis, in an evidence- and consensus-based manner, on the basis of discussions at the Tokyo International Consensus Meeting.

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Table 1. Bacterial culture positive rates in bile (%) in various biliary diseases

	Bile	Non-biliary disease	Chole-lithiasis	Acute cholecystitis	Choledo-cholithiasis (+cholangitis)	Hepatolithiasis (+cholangitis)
Chang (2002)[4]	Gallbladder		17.0	47.0	63.0	70.0
	Bile duct					
Csendes (1996)[5,6]	Gallbladder	0	22.2	46.1		
	Bile duct		23.9	29.0	58.2	93.9
Csendes (1994)[39]	Gallbladder	0	32.0	41.0	58.0	
Maluenda (1989)[2]	Bile duct				76.0	89.0
	Gallbladder	0		43.0 (Chronic; 30)		
Csendes (1975)[40]	Gallbladder wall			47.0 (Chronic; 33)		
Kune (1974)[41]	Gallbladder	0	13.0	54.0	59.0	
	Bile duct					

Table 2. Bacterial species identified in bile of patients with acute cholangitis[2,4–8]

Bacteria	Positive rate in bile (%)
Aerobes	
Escherichia coli	31–44
Klebsiella	8.5–20
Enterobacter	5–9.1
Proteus	1–4.8
Salmonella typhi	0.8–2.6
Salmonella paratyphi	0.8–2.3
Citrobacter	1.6–4.5
Pseudomonas	0.5–7
Streptococcus spp.	2–10
Enterococcus faecalis	2.6–10
Anaerobes	
Clostridium	3–12.7
Bacteroides	0.5–8

Q1. How to detect causative organisms of acute cholangitis?

Bile/blood culture should be performed at all available opportunities (recommendation B).

Table 1 lists the positive rates of bacterial cultures in bile in various biliary diseases. While bile is sterile in individuals without any biliary disease, a positive bile culture is common in various biliary diseases. In patients with acute cholangitis and choledocholithiasis, a positive bile culture is correlated with progression to severe cholangitis and a high mortality rate (level 2b-3b).[1,2] Also, care should be exercised regarding the postoperative occurrence of infective complications in patients with positive bile cultures (level 5).[3] These facts emphasize the importance of early antimicrobial therapy.

It was reported that microbial organisms contained in bile from various biliary diseases were of intestinal bacterial flora origin (Table 2). Aerobic bacteria such as *Escherichia coli*, *Klebsiella, Enterococcus*, and *Enterobacter* are most frequently isolated, whereas *Streptococcus spp.*, *Pseudomonas*, and *Proteus* are less frequently isolated (level 2b-3b).[2,4–8] Although anaerobic bacteria such as *Clostridium* and *Bacteroides* are often isolated, most of these patients have polymicrobial infections with aerobic bacteria (level 5).[9–11] There are reports that anaerobic bacteria are often detected patients with severe acute cholangitis (level 2b-3b).[12–14]

Moreover, it should also be kept in mind for the estimation of causative bacteria in acute cholangitis, whether the infection is community-acquired or hospital-acquired. When it is community-acquired, intestinal microorganisms such as *E. coli*, *Klebsiella,* and *Enterococcus* are likely to be the causative bacteria. By contrast, we have to take into account that, in patients with hospital-acquired type infections, especially those in a postoperative state or those with indwelling stents and malignancies, more resistant organisms, i.e., methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococcus* (VRE), and *Pseudomonas*, are frequently detected as causative microorganisms.

Many patients with cholangitis with a microbial-positive blood culture have the same species of bacteria in blood as those isolated from bile cultures (level 3b),[12] and the positive rate increases with the co-existence of acute cholangitis due to biliary obstruction (level 2b).[1] The blood culture-positive rates in acute cholangitis have been reported to vary from 21% to 71% (level 5).[9–11,15] Patients with bacteremia are frequently resistant to treatment regimens (level 4),[16] and bacteremia is correlated with the duration of hospitalization, the incidence of postoperative renal failure, and the mortality rate (level 2b).[1] These findings underscore the importance of antisepsis therapy, as outlined in the Surviving Sepsis Campaign guidelines of the Society of Critical Care Medicine.[17]

There has been no good-quality evidence to support the importance of blood and bile culture in patients with

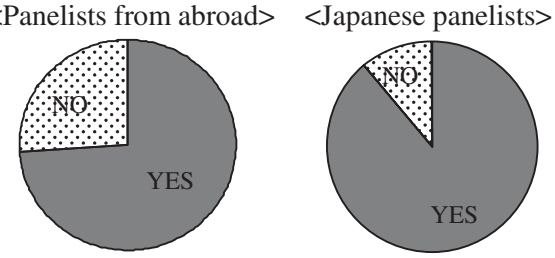

Fig. 1. Responses to the question: "Should bile culture be performed in all patients with acute cholangitis?" Yes, 26 (74%); no, 9 (26%) in 35 overseas panelists, and yes, 17 (89%); no, 2 (11%) in 19 Japanese panelists

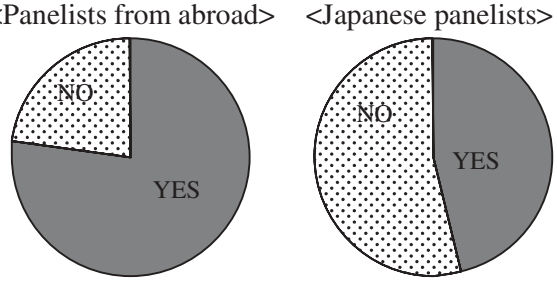

Fig. 2. Responses to the question: "Should blood culture be performed in all patients with acute cholangitis?" Yes, 20 (77%); no, 6 (23%) in 26 overseas panelists, and yes, 12 (46%); no, 14 (54%) in 26 Japanese panelists

acute cholangitis. At the Tokyo Consensus Meeting, we reached a consensus on the importance of bile culture for patients with acute cholangitis (Fig. 1). By contrast, there was a significant discrepancy between Japanese and overseas panelists in regard to the importance placed on blood culture for all patients; while more than half of the overseas panelists agreed on the necessity for blood culture, most of the Japanese panelists disagreed (Fig. 2). Representative reasons for the disagreement were that, usually, blood cultures did not provide any information beyond that provided by bile cultures, and that postoperative acute cholangitis in patients with a choledocho-jejuno anastomosis did not need intensive bacteriological studies. It is, however, rational to rule out bacteremia, when possible, in patients with severe cholangitis, as this would affect the duration of antimicrobial therapy.

Q2. How are antimicrobial agents used for patients with acute cholangitis?

- **Antimicrobial agents should be administered to all patients diagnosed as having acute cholangitis (recommendation A); the Antimicrobial agents should be administered as soon as the diagnosis of acute cholangitis is suspected or established.**
- **For patients with moderate (grade II) or severe (grade III) acute cholangitis, antimicrobial agents should be administered for a minimum duration of 5–7 days. More prolonged therapy could be required, depending on the presence of bacteremia and the patient's clinical response, judged by fever, white blood cell count, and C-reactive protein, when available (recommendation A).**
- **For patients with mild (grade I) acute cholangitis, the duration of antimicrobial therapy could be shorter (2 or 3 days) (recommendation A).**

An important and fruitful discussion was held regarding the duration of antimicrobial therapy for patients with acute cholangitis (see "Discussion"). In summary, patients with moderate (grade II) or severe (grade III) acute cholangitis should receive a minimum duration of therapy of 5–7 days, and then, based on the anatomy of the disease and the presence of bacteremia, and their clinical responses, patients may need more prolonged therapy. However, for the large group of patients with mild (grade I) cholangitis, 2 or 3 days of antimicrobial therapy is likely to be sufficient. Needlessly prolonged antimicrobial therapy risks adverse reactions to the antimicrobials, and intensifies pressure for the development and acquisition of resistant bacteria.

Q3. What are the most important factors for consideration in antimicrobial drug selection?

(1) Antimicrobial activity against causative bacteria
(2) Severity of cholangitis
(3) Presence/absence of renal and hepatic disease
(4) Past history of antimicrobial administration to the patient
(5) Local susceptibility patterns (antibiogram) of the suspected causative organisms
(6) Biliary penetration of the antimicrobial agents.

The dose of the antimicrobial agent should be reduced for patients with reduced renal function. Because most cephalosporin, penicillin, aminoglycoside, and carbapenem antimicrobial drugs are excreted by the kidneys, the dose is reduced for patients with nephropathy and decreased renal function. *The Sanford guide to antimicrobial therapy*, 2003[18] and *Goodman and Gilman's the pharmacological basis of therapeutics*[19] recommend that renal function be estimated by the following formula:

Creatinine clearance predicted from serum creatinine (×0.85 for females) = (140 – age)(optimum body weight (kg)) / (72 × serum creatinine mg/dl)

where male optimum body weight is 50.0 kg + 0.91 kg/cm (150 cm and taller) and female optimum body weight is 45.5 kg + 0.91 kg/cm (150 cm and taller).

Drug dosage adjustment should be done in patients with decreased renal function. *The Sanford guide to antimicrobial therapy* and *Goodman and Gilman's the pharmacological basis of therapeutics* should be consulted (recommendation A).

Drug dosage adjustment for ceftriaxone is not necessary in patients with renal failure. But dose adjustment of ceftriaxone is indicated for patients with severe hepatic impairment.[18] In addition, when biliary obstruction that blocks the enterohepatic circulation of bile is present, the administration of third- and fourth-generation cephalosporins may replace the intestinal flora and disturb vitamin K absorption, in turn risking coagulopathic hemorrhage. This phenomenon, leading to bleeding tendency, can be enhanced in patients with comorbid liver diseases or liver failure due to severe acute cholangitis. Intravenous administration of vitamin K may be indicated in these situations.

Q4. Should biliary penetration be considered important in the selection of therapeutic antimicrobials in acute cholangitis?

Biliary penetration should be considered in the selection of antimicrobial agents in acute cholangitis (recommendation A).

It has been debated whether antimicrobials with good biliary penetration should be recommended for acute cholangitis. Indeed, there was a common belief, particularly in Japan, that antimicrobial agents with excellent biliary penetration are more effective for the treatment of acute cholangitis. However, there are no clinical or experimental data to strongly support the recommendation of antimicrobials with excellent biliary penetration for these patients. In fact, in most patients with acute cholangitis, biliary obstruction is usually present, and antimicrobial drugs may not be detected in bile even if they demonstrate excellent biliary excretion in normal conditions (level 3b–4).[20–27]

Nevertheless, at the Consensus Meeting, we reached a consensus that the importance of biliary penetration should be emphasized for the empirical selection of antimicrobial agents (Fig. 3). For details, see "Discussion at the Tokyo International Consensus Meeting." In Table 3, we list antimicrobial agents with good biliary penetration.

Q5. What are the results of clinical trials regarding antimicrobial therapy in acute cholangitis?

The combination of ampicillin and an aminoglycoside was regarded as a standard regimen for cholangitis in the 1980s (level 4–5),[28,29] and most randomized controlled trials (RCTs) have concluded that recently developed antimicrobial drugs had effectiveness and usefulness equivalent to that of ampicillin and aminoglycosides (Table 4) (level 2b).[30–35] Therefore, according

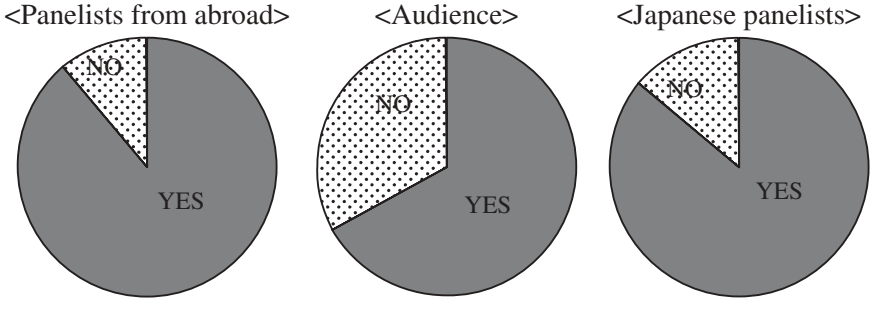

Fig. 3. Responses the question: "Should the biliary penetration of antimicrobial agents be considered important in the in selection in moderate (grade II) or severe (grade III) acute cholangitis?" Yes, 24 (89%); no, 3 (11%) in 27 overseas panelists; yes, 18 (67%); no, 9 (33%) in 27 Japanese panelists; and yes, 55 (86%); no, 9 (14%) in 64 audience members

Table 3. Intravenous antimicrobial drugs with good biliary penetration (level 4)[18]

Penicillins	Piperacillin, aspoxicillin, piperacillin/tazobactam, ampicillin
Cephalosporins	
1st Generation	Cefazoline
2nd Generation	Cefmetazole, cefotiam, flomoxef
3rd, 4th Generation	Cefoperazone/sulbactam,[20] ceftriaxone,[42] cefozopran, cefpirome, ceftazidime, cefoperazone
Fluoroquinolones	Ciprofloxacin,[20] Pazufloxacin
Monobactams	Aztreonam[21]
Lincosamides	Clindamycin[38]

Table 4. Comparative tests clinical of antimicrobial drugs in acute cholangitis

Authors (Year)	Subjects	Administered antimicrobials	Clinical cure rate	Statistical significance
Muller (1987)[30]	Cholangitis	Ampicillin+ tobramycin	85% (17/20)	
		Piperacillin	60% (9/15)	NS
		Cefoperazone	56% (10/18)	$P < 0.05$
Gerecht (1989)[31]	Cholangitis	Mezocillin	83% (20/24)	$P < 0.01$
		Ampicillin + gentamicin	41% (9/22)	
Thompson (1990)[32]	Cholangitis	Piperacillin	70%	NS
		Ampicillin + tobramycin	69%	
Chacon (1990)[33]	Cholangitis + cholecystitis	Pefloxacin	98% (49/50)	NS
		Ampicillin + gentamicin	95.7% (45/47)	
Thompson (1993)[34]	Cholangitis + cholecystitis	Cefepime	97.5% (78/80)	NS
		Mezlocillin + gentamicin	100% (40/40)	
Sung (1995)[35]	Cholangitis	Ciprofloxacin	85% (39/46)	NS
		Ceftazidime + ampicillin + metronidazole	77% (34/44)	

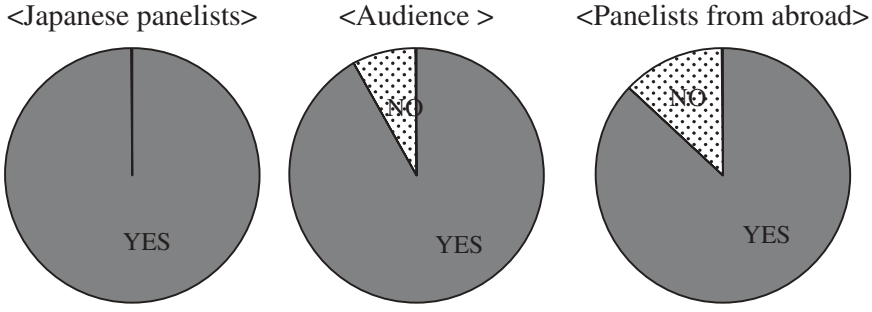

Fig. 4. Reponses to the question: "Should empirically administered antimicrobial drugs be changed for more appropriate agents, according to the identified causative microorganisms and their sensitivity to antimicrobials?" Yes, 30 (100%) in 30 Japanese panelists; yes, 21 (87%); no, 3 (13%) in 24 panelists from abroad; and yes, 61 (92%); no, 5 (8%) in 66 audience members

to the clinical trials available so far, piperacillin, ampicillin and an aminoglycoside, and several cephalosporins, are recommended for the treatment of acute cholangitis.

However, at present antimicrobial agents widely used for acute cholangitis, including penicillin/β-lactamase inhibitors, carbapenems, and the third- and fourth-generation cephalosporins, have not been tested in these RCTs. In this regard, we recommend the alternative regimens for antimicrobial agents stated in the Tokyo Guidelines. The recommendations were reached in a consensus-based manner, as follows.

Q6. What are the current recommendations for antimicrobial therapy in acute cholangitis?

- **Antimicrobial drugs should be selected according to the severity assessment (recommendation A).**
- **Empirically administered antimicrobial agents should be changed for more appropriate agents according to the identified causative microorganisms and their sensitivity to antimicrobials (recommendation A).**

In the Infectious Diseases Society of America (IDSA) guidelines for intraabdominal infections, the selection of antimicrobial agents is based on the severity of the infection.[36] In the Tokyo Guidelines, the selection of antimicrobial agents is based on the severity of acute cholangitis. However, it should be emphasized that there is little high-level evidence that supports this notion.

It was widely accepted at the Consensus Meeting that empirically administered antimicrobial agents should be changed for more appropriate agents according to the identified causative microorganisms and their sensitivity to antimicrobials (Fig. 4).

In any guidelines, recommended doses of antimicrobials, ideally based on body weight, should also be provided. However, the dose administered can vary in each country, depending on medical practices and legal regulations. For instance, it was known and discussed at the Consensus Meeting that the legally approved doses of antimicrobials in Japan are different from those used in the United States and Europe. Therefore, recommended doses of antimicrobial agents are not provided in the Tokyo Guidelines, and doses should be determined according to local rules and regulations. Similarly, the cost of the agents, which should also be discussed, varies in

different countries and was not addressed in the Tokyo Guidelines.

Antibacterials selected for the three grades of acute cholangitis

Mild (grade I) acute cholangitis

Mild (grade I) cases of the disease are often caused by a single intestinal organism, such as *E. coli*, and therefore monotherapy with one of the following antimicrobial drugs should be chosen. Because intestinal organisms producing β-lactamase, which are resistant to penicillins and cefazoline, are likely to be detected, the use of a penicillin/β-lactamase inhibitor, such as piperacillin/tazobactam,[37] or ampicillin/sulbactam is recommended (see Table 5).

Moderate (grade II) and severe (grade III) acute cholangitis (Table 6)

Patients with moderate (grade II) and severe (grade III) disease are often infected with multiple and/or resistant organisms (level 2b–3b).[3,12,14] Thus, third- and fourth-generation cephalosporins, with a wide antimicrobial spectrum, as well as broadspectrum penicillin/β-lactamase inhibitors, are recommended as the drug of first choice. Depending on the local susceptibility patterns (antibiogram), if the drug of first choice is ineffective, fluoroquinolones and carbapenems can be used.

It should be emphasized that the inappropriate use or overuse of third- and fourth-generation cephalosporins and carbapenems would likely result in the emergence of resistant bacteria. For instance, it has been reported that some *E. coli* strains acquire resistance to ampicillin/sulbactam.

Piperacillin/tazobactam is strongly recommended when *Pseudomonas* spp. are considered as the causative organisms. Of note, the ratio of penicillin to tazobactam is different in Japan (4:1) from that in the United States (8:1).

Table 5. Antibacterials for grade I acute cholangitis

First-generation cephalosporins	Cefazoline
Second-generation cephalosporins	Cefmetazole, cefotiam, oxacephem, flomoxef
Penicillin/β-lactamase inhibitor	Ampicillin/sulbactam

Q7. Is there any difference between Japan and the United States in the use of antimicrobial agents for acute cholangitis?

On the basis of pharmacokinetics and pharmacodynamics, there is a significant difference between the United States and Japan in antimicrobial dosing regimens. For details, see "Discussion", for discussions held at the Tokyo International Consensus Meeting.

As a consequences of the inappropriate dosing regimens in Japan, inadequate clinical responses may be seen in Japanese patients. Moreover, the overuse of broad spectrum agents such as carbapenems has been another problem in Japan. Unpublished data from a major global pharmaceutical company indicate that Japan consumes half of the carbapenems produced worldwide. This could be evidence of the overuse of carbapenems in Japan.

Q8. How should antimicrobial drugs be administered for acute cholangitis associated with biliary obstruction?

The presence of biliary obstruction may significantly influence the biliary penetration of the antimicrobial, as well as acting as a persistent source of infection. Therefore, patients with acute cholangitis, especially those with severe (grade III) disease, should have immediate biliary drainage along with appropriate antimicrobial therapy (recommendation A).

When biliary obstruction is present, even an antimicrobial drug with excellent biliary excretion may not enter the bile tract (level 3b–4).[20–27] The active transfer of antimicrobial drugs into bile is not restored early after the biliary obstruction has been relieved (level 4).[25,38] Therefore, immediate biliary drainage, as well as the admin-

Table 6. Antibacterials for moderate (grade II) and severe (grade III) acute cholangitis

First options	
Wide spectrum penicillin/β-lactamase inhibitor (as single agents)	Ampicillin/sulbactam, piperacillin/tazobactam
Third- and fourth-generation cephalosporins	Cefoperazone/sulbactam, ceftriaxone, ceftazidime, cefepime, cefozopran
Monobactams	Aztreonam
One of above + metronidazole (to cover anaerobes)	
Second options	
Fluoroquinolones	Ciprofloxacin, levofloxacin, pazufloxacin
One of above + metronidazole (to cover anaerobes)	
Carbapenems	Meropenem, imipenem/cilastatin, doripenem

istration of antimicrobials, is crucial in view of controlling the source of infection.

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

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Discussion at the Tokyo International Consensus Meeting

The issue of the Significant difference between the United States and Japan in antimicrobial dosing regimens

Harumi Gomi (Japan): In the United States, ampicillin/sulbactam — one of the most commonly used agents for intraabdominal infections — the regular dosage for adult patients with normal renal function is 3 g intravenously every 6 hours, and the total dosage is 12 g per day. On the other hand, in Japan, the legally approved dosage is 3 g intravenously twice a day, meaning the maximum daily dose is 6 g. Another example is piperacillin/tazobactam. The FDA-approved dosage is 3.37–4.5 g intravenously every 6–8 h, meaning 13.5–17.5 g per day. On the other hand, in Japan, the regular dose or legally approved dose is 2.5 g intravenously twice a day, meaning 5 g per day is the maximum. [In regard to] aminoglycosides: [for] gentamicin; in the United States, the regular dosage is 1–1.7 mg per kg every 8 h, or 4.5–5.0 mg per kg every 24 h as a once-daily dosage. Therefore for adult patients with a body weight of up to 50 kg, the daily dose is 225–250 mg. But again, in Japan, the maximum dose is 80–100 mg per day, regardless of body weight. So there is a significant issue and difference.

How long should antimicrobial agents be given for patients with acute cholangitis?

Joseph S. Solomkin (USA): The other point I will make, just to relay our experience in North America, is that there is increasing emphasis on shortened duration of therapy, and typically now the standard recommendation for treatment would be approximately 7–10 days until the patient is afebrile, has resolved their infection clinically, and is taking oral intake. There are a lot of people who think that that is too long; that in fact 5 days may be the optimal therapy, so I think that is another very important area to look at, because certainly the longer patients are on these very broadspectrum agents, the greater the potential harm in terms of superinfection and toxicity.

Henry A. Pitt (USA): That was my point as well. I give a short course if there is no bacteremia, and then try to stop quickly, but I give a real course of 7–10 days if there is bacteremia.

Joseph Solomkin: Has anybody . . . I would just like to ask one question since I think you people have more experience than I do with this; if a patient has an episode of cholangitis, is short-course treatment — say 5 days — is there a risk they will develop liver abscesses? So when we are talking about the duration of therapy, should that be a factor in it?

Henry Pitt: I think it depends a lot on the exact clinical situation. I mean, we see cholangitis most often now in patients who have indwelling stents, who come in and they get their stent changed, and then the bile is flowing again and the cholangitis goes away quickly, and they either have had a liver abscess or not when they come in, and you figure that out, if they do not respond to the usual therapy and/or they have blood cultures.

Serafin C. Hilvano (Philippines): I would also agree that we set a minimum number of days for the therapy.

Thomas R. Gadacz (USA): There are a lot of specifics that have been brought up, such as liver abscess, you would treat a patient for a long period of time. Patients where the acute cholangitis may be simply be due to a plugged-up stent which gets changed very quickly, in which case short-term therapy would be probably very appropriate. So I think that the absolute determination here is not one that that is trying to be a solution, but really a guideline and that is stated in the question, "should be." The specific situation then could be altered depending upon what the exact condition is.

Should biliary penetration be considered important in the selection of therapeutic antimicrobials in acute cholangitis?

Henry Pitt: The first point has to do with biliary penetration. I think that there is a spectrum of disease, and initially before drainage the biliary penetration probably makes no difference, and having good blood levels is very important. But I think after drainage, I imagine, although there are no good data, that their biliary penetration gradually goes up and that there may be some advantage 3 or 4 days into an illness when someone is very sick, I do not know.

Chen-Guo Ker (Taiwan): In cases of obstruction, the penetration of antibiotics was very low, in the studies more than 10 years ago. So it is better to give the drainage in the first acute phase. But during the acute phase, we have to keep the antibiotics for prevention of the systemic bacteremia; so that you do not mention. It is not necessary to care about the penetration into the bile. But another thing which is very important; antibiotic penetration into the bile, this should be combined with the ligand-specific protein. So in cases of patient with low albuminemia, last penetrated into the bile must be very low. So we have to care about the timing of the giving of antibiotics and what kind of antibiotics we use. It is my opinion. Thank you.

(Voting was done)

Joseph Solomkin: You know, I think the numbers, particularly from our Japanese hosts, are strong enough so that in the guidelines we should say or make the statement that it is the opinion of the Japanese that biliary penetration is important.

Steven M. Strasberg (USA): But is the other point not given that what we are here to do is that there is not good evidence from the literature of the importance of this factor?

Atsushi Tanaka (Japan): Well, as I have said, there is very little evidence suggesting the importance of this.

Steven Strasberg: Well, that is what I mean; there is very little evidence, so it is really a point that we cannot make a rational decision about it, so it is about as authoritarian as you can get.

Joseph Solomkin: That is why it was brought up for discussion, but I think here that Dr. Tanaka made the point very clearly that that was the case; that the superiority just is not there, it has not been demonstrated. Conversely, if you have a group of practitioners who strongly believe something that is not critical to the health of the patient, I would be more concerned of risking their not using the guidelines at all. That is a very big question.

Yoshifumi Kawarada (Japan): Sir. I have to ask Dr. Gomi, what do you think about the biliary penetration by antibiotics in acute cholecystitis?

Harumi Gomi: Well, since all my training was done in the United States, I am more towards the United States position. This means that I do not consider the penetration of the biliary tract.

Yoshifumi Kawarada: Yes, I had the same opinion. I had a bias. I was educated in the United States, always being against the penetration, it is not so important; but for Japanese people, 71% say "Yes."

Steven Strasberg: I find it very difficult to understand how we can publish a guideline that says anything that is not a reflection of the best available evidence; and think that whether someone is going to follow a guideline or not is a second degree of relevance, or a second degree of what we should be considering. I do not know this literature, but if the literature says that drugs that do penetrate the biliary epithelium do not do any better than drugs that do not penetrate the biliary epithelium, then just as you have said before, the evidence is that it is a factor of no importance or minor importance, and I think the guidelines should say that.

Joseph Solomkin: The reservation — I appreciate you saying that — the reservation I have is that these are consensus guidelines, so that they are guidelines that basically . . . these guidelines, as far as I am concerned, or were I to write them would say, "The evidence is such and such; at the consensus meeting, nonetheless, the panelists believe because of current common practice, that such and such is okay." I think you have to do both things; state the facts and then I do not think you can discredit the consensus.

Henry Pitt: Part of the problem is that we have no good evidence. The paper that is quoted as the best evidence is Michael Keith-Floyd's paper that was published in 1974, and it was a retrospective analysis of whether people were treated with gentamicin or not. That is not good evidence either. So we have to make a recommendation, and then we say it is based on A-, B-, C-, D-, or E-level evidence, and this will be a lower-level evidence recommendation.

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Journal of HBP Surgery

Methods and timing of biliary drainage for acute cholangitis: Tokyo Guidelines

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Abstract
Biliary drainage is a radical method to relieve cholestasis, a cause of acute cholangitis, and takes a central part in the treatment of acute cholangitis. Emergent drainage is essential for severe cases, whereas patients with moderate and mild disease should also receive drainage as soon as possible if they do not respond to conservative treatment, and their condition has not improved. Biliary drainage can be achieved via three different routes/procedures: endoscopic, percutaneous transhepatic, and open methods. The clinical value of both endoscopic and percutaneous transhepatic drainage is well known. Endoscopic drainage is associated with a low morbidity rate and shorter duration of hospitalization; therefore, this approach is advocated whenever it is applicable. In endoscopic drainage, *either* endoscopic nasobiliary drainage (ENBD) or tube stent placement can be used. There is no significant difference in the success rate, effectiveness, and morbidity between the two procedures. The decision to perform endoscopic sphincterotomy (EST) is made based on the patient's condition and the number and diameter of common bile duct stones. Open drainage, on the other hand, should be applied only in patients for whom endoscopic or percutaneous transhepatic drainage is contraindicated or has not been successfully performed. Cholecystectomy is recommended in patients with gallbladder stones, following the resolution of acute cholangitis with medical treatment, unless the patient has poor operative risk factors or declines surgery.

Key words Cholangitis · Biliary · Drainage · Endoscopy · Percutaneous · Sphincterotomy · Guidelines

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Introduction

Acute cholangitis presents with a wide spectrum of severity, ranging from relatively mild cases to severe cases associated with hypotension and disturbed consciousness. It has been reported that when no appropriate biliary drainage was available 20–30 years ago, the mortality of acute cholangitis with conservative treatment was extremely high (Table 1). There has been no randomized controlled trial (RCT) comparing conservative treatment and biliary drainage. However, it is evident that many patients with acute cholangitis cannot be saved by conservative treatment alone.

Biliary drainage is a radical method to relieve cholestasis, a cause of acute cholangitis, and takes a central part in the treatment of acute cholangitis. This article reviews articles in the literature on biliary drainage methods and discusses the methods and timing of biliary drainage for acute cholangitis, in terms of the principles

of evidence-based medicine, in a question and recommendation format. The recommendations are defined according to discussion at Tokyo Consensus Meeting.

Q1. How do we select the mode of biliary drainage — endoscopic vs percutaneous vs open?

Endoscopic biliary drainage (recommendation A).

Percutaneous transhepatic biliary drainage (recommendation B).

Biliary drainage can be achieved by three different procedures: endoscopic, percutaneous transhepatic, and open drainage. The safety and usefulness of endoscopic drainage have been proved by many studies (level 2b)[3] (level 4).[4–6] A randomized controlled trial (RCT)[3] was conducted to compare endoscopic and open drainage in 82 patients with severe acute cholangitis with hypotension and disturbed consciousness. This RCT demonstrated that the morbidity and mortality of endoscopic nasobiliary drainage (ENBD) + endoscopic sphincterotomy (EST; $n = 41$) were significantly lower than those of T-tube drainage under laparotomy ($n = 41$), concluding that endoscopic drainage was safer and more effective than open drainage (Table 2) (level 2b). Although there are no recent reports on open drainage, Sawyer and Jones[7] describe that endoscopic or interventional radiological drainage is superior to open drainage.

Chen et al.[8] performed percutaneous transhepatic biliary drainage (PTBD) in 56 acute cholangitis patients, and observed noticeably improved clinical conditions in 46 patients (82.1%), with disappearance of fever within 18–24 h (level 4). Pessa et al.[9] also performed PTBD, in 42 acute cholangitis patients, and reported a success rate of 100%, morbidity rate of 7%, and mortality rate of 5% (level 4). Though the usefulness of percutaneous transhepatic drainage is widely recognized, all of the previous reports were retrospective case-series studies (level 4).[8–16]

As there is no RCT comparing endoscopic and percutaneous drainage, a definitive conclusion on the better procedure has not been reached. However, considering the rare occurrence of serious complications such as intraperitoneal hemorrhage and biliary peritonitis,[4–6] and the shorter duration of hospitalization,[17] endoscopic drainage is preferred whenever it is available and applicable (level 4)[17,18] (level 3a).[19–21] In short, as both procedures require experienced hands, the drainage method selected should be contingent upon the availability of resources and staff, so that the drainage can be delivered successfully with a good outcome.

Results at Tokyo Consensus Meeting

Most panelists from Japan and abroad preferred endoscopic drainage (Fig. 1).

Q2. What procedure should be used for endoscopic biliary drainage? External (nasobiliary drainage) or internal drainage? Also, what are the criteria for the addition of endoscopic sphincterotomy (EST) vs no EST?

Either ENBD or biliary tube stent placement can be used.

Addition of EST should be determined according to the patient's condition and the operator's skill.

Two RCTs (level 2b)[22,23] comparing ENBD and biliary tube stent placement showed no significant difference in success rate, effectiveness, or morbidity. Another study[22] revealed that the incidence of tube troubles such as removal of the tube by patients themselves tended to be higher with ENBD, and the patient's level of discomfort was significantly lower with the stent placement. From these findings, for patients who are likely to remove the ENBD tube by themselves, stent placement is preferable.[22]

Table 1. Mortality of acute cholangitis patients peceiving conservative treatment

Author	Mortality rate with conservative therapy
O'Connor et al.[1]	87%
Welch and Donaldson[2]	100%

Table 2. Drainage for acute cholangitis: endoscopic vs open drainage[3]

Results	Endoscopic	Open	Relative risk reduction
Mortality	10%	32%	69%
Complication	34%	66%	48%
Artificial respiration installation	29%	63%	54%

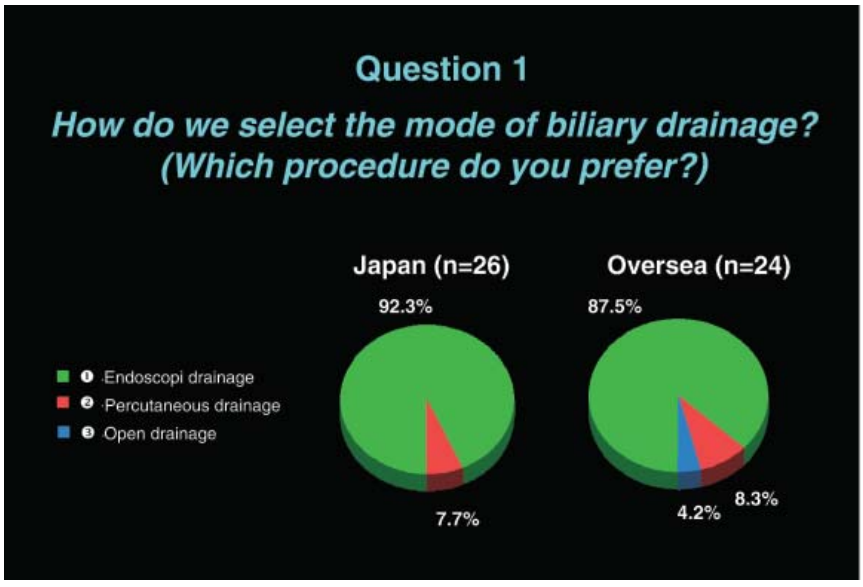


Fig. 1.

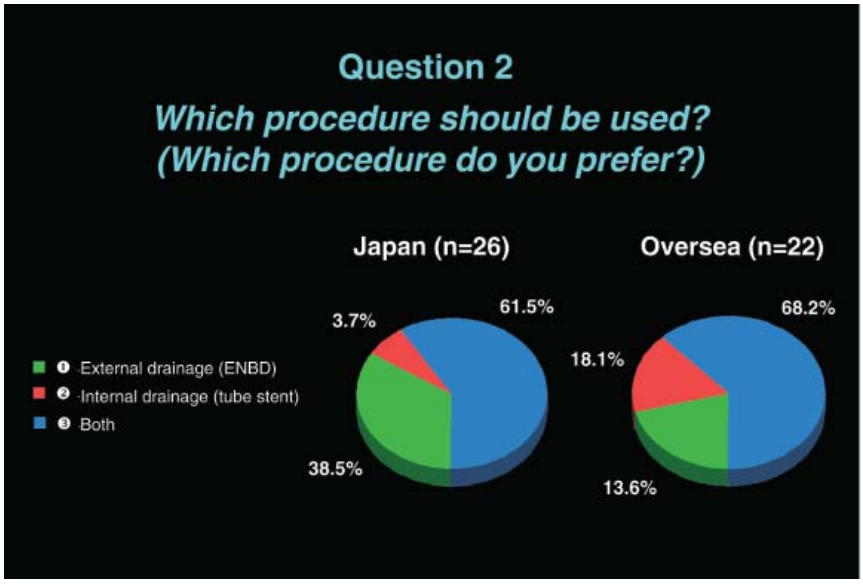


Fig. 2.

Endoscopic biliary drainage methods applicable for choledocholithiasis-induced acute cholangitis, the most frequently encountered disease in the clinical setting, include EST alone, EST followed by lithotomy, and ENBD or biliary tube stent placement using a plastic tube with or without EST, but there is no RCT comparing these methods. There are two reports of case-series studies (level 4),[24,25] which examined whether or not EST should be added to ENBD or biliary tube stent placement (Table 3). They indicated that there was no significant difference in the success rate and effectiveness of drainage between these two methods, but complications including hemorrhage were observed more frequently in patients who underwent EST. Accordingly, for critically ill patients in whom emergent drainage is essential, ENBD or stent placement without EST is preferable, and one-stage choledocholithotomy requiring EST is not recommended. The performance of choledocholithotomy following EST should be determined by taking both the patient's condition and the number and diameter of stones into account.

Results at Tokyo Consensus Meeting

About two-thirds of the panelists agreed that either ENBD or biliary tube stent placement could be used (Fig. 2). As to the addition of EST, more than half of the panelists mentioned that EST was essential in principle, but that its use depended on the patient's condition and the operator's skill (Fig. 3).

Table 3. Endoscopic biliary drainage: with EST vs without EST

Author	No EST added				EST added			
	No. of patients	Success rate (%)	Effectiveness %	Incidence of complications (%)[a]	No. of patients	Success rate (%)	Effectiveness (%)	Incidence of complications (%)[a]
Sugiyama and Atomi (1998)[24] (ENBD; 7-Fr)	93	96	94	2	73	95	92	11
Hui et al. (2003)[25] (Stent; -Fr)	37	86	100	3	37	89	100	11

[a] Complications associated with technique, such as bleeding and pancreatitis

Q3. What are the indications for open drainage?

Open drainage should only be used in patients for whom endoscopic or percutaneous transhepatic drainage is contraindicated or those in whom it has been unsuccessfully performed. In such difficult conditions, the primary goal is to decompress the biliary tract expeditiously. It is important to emphasize the shortening of operative time and the minimizing of surgical invasiveness. For these reasons, it is recommended to complete the operation quickly by placing a T-tube without spending a long time on lithotomy[26] (level 4).

Q4. Is prophylactic cholecystectomy necessary after choledocholithiasis has been successfully treated in acute cholangitis?

Cholecystectomy is indicated after the resolution of acute cholangitis (recommendation B).

Boerma et al.[27] conducted an RCT (level 2b) to assess the clinical value of prophylactic laparoscopic cholecystectomy in patients whose choledocholithiasis was successfully treated with EST (all patients had gallbladder stones). Symptoms related to cholecystitis appeared in 27 of 59 patients (46%) who had not undergone prophylactic laparoscopic cholecystectomy, and eventually 22 of the 27 underwent cholecystectomy. Thus, Boerma et al. concluded that prophylactic cholecystectomy was of clinical value.

It has been reported that the incidence of cholecystitis in patients whose gallbladders were left with stones after EST was 7.6%–22% (level 2b)[28–31] (Table 4). This incidence is not significantly different from the incidence of cholecystitis in patients with asymptomatic cholecystolithiasis (15.5%–51%); therefore, prophylactic cholecystectomy might be unnecessary. The objective here is to prevent the subsequent recrudescence of severe acute cholangitis or acute cholecystitis with attending high fatality. In patients with an acalculous gallbladder, the incidence of cholecystitis is low, around 1%, so that no cholecystectomy is required (level 2b)[28–31] (Table 4).

Results of discussion about the "Timing of biliary drainage" at the Tokyo Consensus Meeting

As to the issue of timing, there are few references leading to evidence-based recommendations; therefore, attempts were made to obtain consensus from the panelists after the discussion.

Consensus was reached regarding severe (Fig. 4) and mild acute cholangitis (Fig. 6), but not on moderate acute cholangitis (Fig. 5).

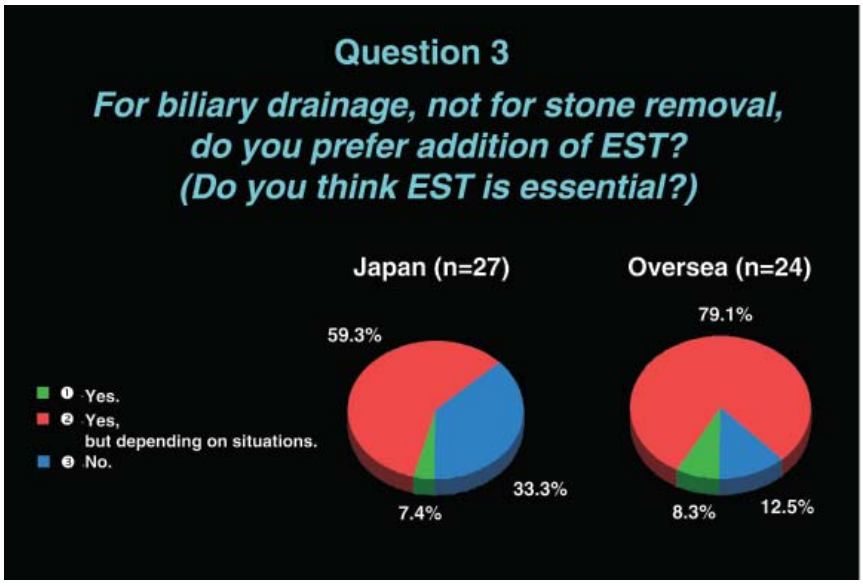


Fig. 3.

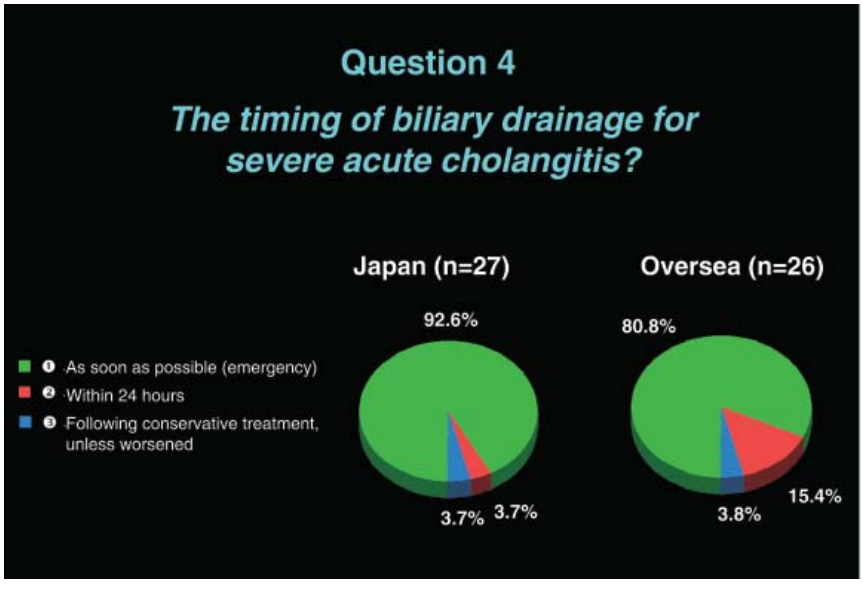


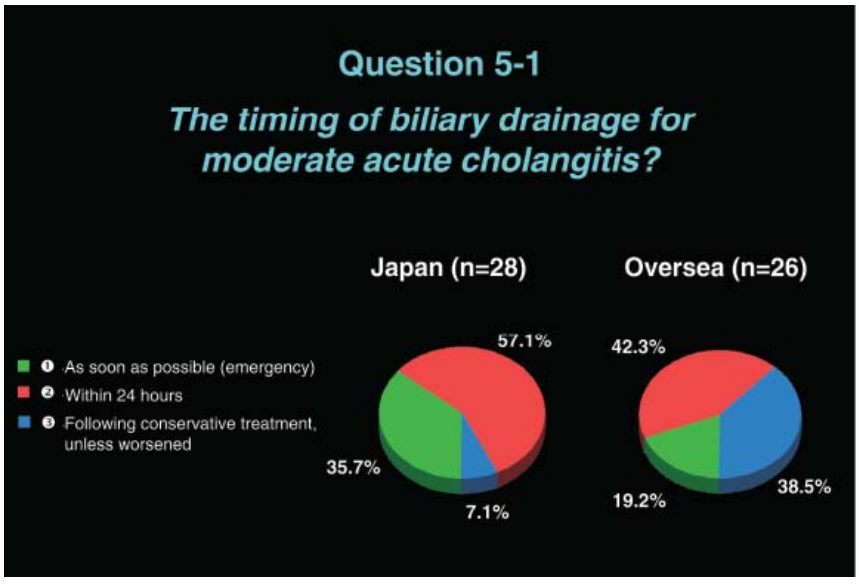
Fig. 4.

Table 4. Incidence of acute cholecystitis after endoscopic treatment of choledocholithiasis

Calculous gallbladder	Acalculous gallbladder	Average observation period (years)
5.8% (11/190)	—	6.8[28a]
7.6% (34/448)	1.2% (3/246)	7.5[29]
12% (2/17)	0% (0/15)	14.5[30]
22% (7/32)	1% (1/88)	10.2[31]

[a] Whether or not the whole population had calculous gallbladders is unknown

a


Question 5-1
The timing of biliary drainage for moderate acute cholangitis?
Japan (n=28)
Oversea (n=26)
❶ As soon as possible (emergency)
❷ Within 24 hours
❸ Following conservative treatment, unless worsened
57.1%
35.7%
7.1%
42.3%
19.2%
38.5%

b

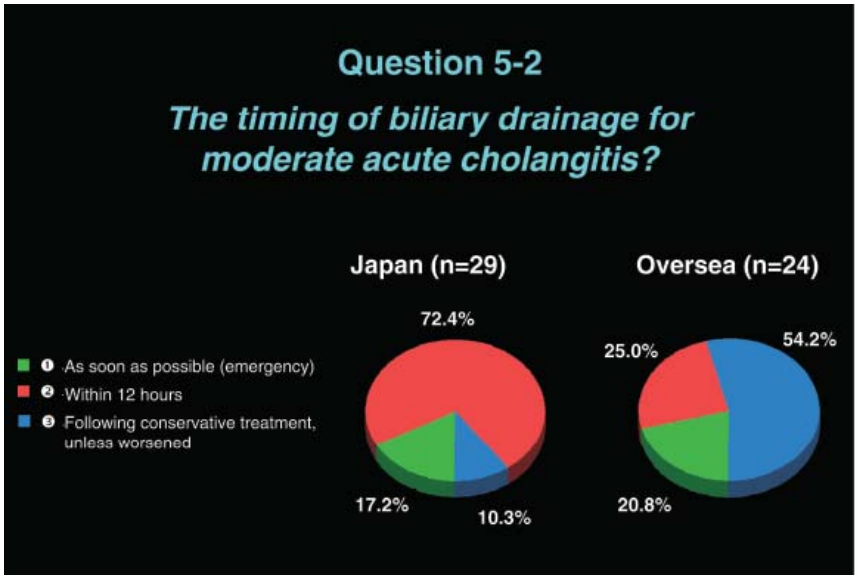

Question 5-2
The timing of biliary drainage for moderate acute cholangitis?
Japan (n=29)
Oversea (n=24)
❶ As soon as possible (emergency)
❷ Within 12 hours
❸ Following conservative treatment, unless worsened
72.4%
17.2%
10.3%
25.0%
54.2%
20.8%

Fig. 5.

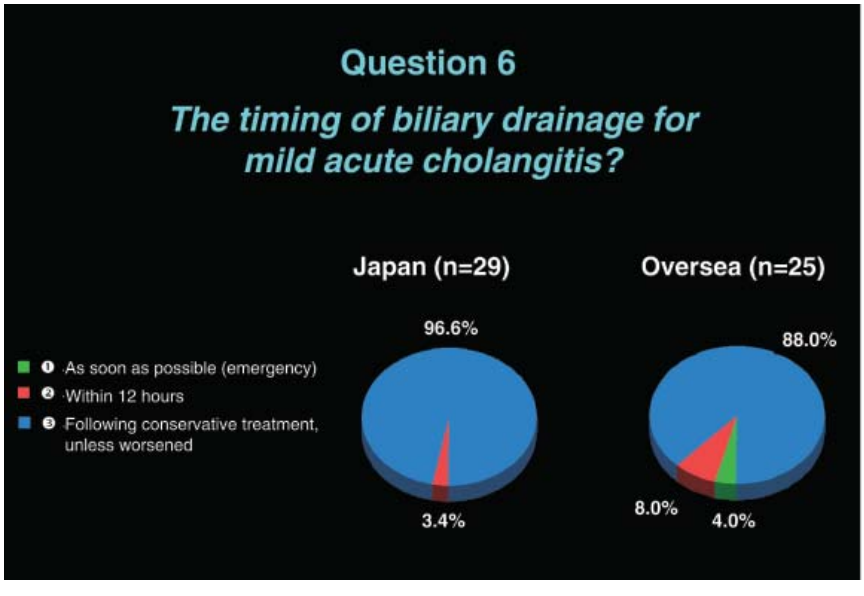

Question 6
The timing of biliary drainage for mild acute cholangitis?
Japan (n=29)
Oversea (n=25)
❶ As soon as possible (emergency)
❷ Within 12 hours
❸ Following conservative treatment, unless worsened
96.6%
3.4%
88.0%
8.0%
4.0%

Fig. 6.

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Discussion at the Tokyo Consensus Meeting

Selection of the mode of biliary drainage

Philippus C. Bornman (South Africa): Thank you very much for your presentation, Dr. Nagino. The first question is "*How do we select the mode of biliary drainage?*" and I would like to focus only on choledocholithiasis and also then bearing in mind that expertise, as well as facilities, are equal at a given institution. So we are going to ask them three questions: should it be endoscopic drainage, percutaneous, or open drainage. But before

we do that, could we please have some comments from our panelists both overseas and local please.

Masato Nagino (Japan): Before selecting such kind of interpretation I do keep in mind the level of biliary stenosis, proximal or distal.

Philippus C. Bornman: Yes, I think that it is an important one and maybe we should — we will certainly bear that in mind and we should come back to that, but if we exclude patients with biliary strictures and we are only talking about patients with choledocholithiasis that is our first question please. No infected stones — we will get to that later on.

Edward C.S. Lai (Hong Kong): I think to start off with, it will be important to differentiate between patients with common bile duct stone and those without. Because these are two very important situations in which the management can be totally different. I know that, Mr. Chairman, you are trying to confine it to stones. But I would like to have a bit of discussion on non-stone situations as well at the end if you have time.

Philippus C. Bornman: Please, we certainly will do that and I think we will take it immediately after we have made our first choice. OK, shall we then go to the vote and shall we start with our Japanese panel of experts and they will indicate to us one, two, or three. Could you please vote now; full house. Good, right, let us first look at the Japanese results. That is not entirely surprising, and then onto the overseas experts (refer to Fig. 1).

From this we can conclude that, in the setting of patients with bile duct stones, without intrahepatic stones without strictures, the preferred procedure is endoscopic drainage. I would like to get some comments. I can see 8% mentioned percutaneous drainage, so there are clearly some situations where the percutaneous drainage will be preferred. Can we get some comments from those who joined the 8% group please?

Serafin C. Hilvano (Philippines): We start off with a compromise, in our institution. We usually prefer the percutaneous drainage first then shift to an endoscopic, enlarging the route — the access — with the use of a cholangioscope so that is sort of a compromise. We start with a percutaneous then shift to a cholangioscope.

Philippus C. Bornman: May I ask, do you have similar endoscopic facilities at your institution or are you more familiar with the percutaneous techniques and its availability?

Serafin C. Hilvano: That is, our colleagues in surgery still lack the skill that our Japanese colleagues have. That is probably the limitation that we are limited to.

Philippus C. Bornman: Thank you for that comment. Can we have some more comments on the percutaneous approach? Joseph, would you like to take it up.[2] Can I ask—can I put it to you this way. At our institution although we have both available, we tend to go for the percutaneous technique in a small select [group] of patients with severe cholangitis and those patients with comorbid disease, because to use conscious sedation and go to a facility at which you do not have all those facilities for resuscitation, we feel that, perhaps, a percutaneous approach in those patients perhaps is a safer procedure, given our facilities and the risks of bleeding and so on; so I will put it as a provocative statement. The other point, of course, is that percutaneous drainage is a secure form of drainage, you are sure that this system is drained, whereas sometimes with the endoscopic one, and we will come to that, you are not always sure if your nasobiliary drain is in position or your stent is functioning properly. Perhaps we can have some comments on that please. Henry, I saw you moving your head sideways — could you comment on that please.[2]

Henry A. Pitt (USA): There may be, I think, some rare circumstances, local circumstances, where percutaneous would be an advantage here. But I think that, all else being equal, which is how you asked the question, equal expertise, I agree with the vast majority.

Internal (tube stent) or external (nasobiliary) drainage

Philippus C. Bornman: The second question we will address is: "*Which procedure do you prefer, internal (tube stent) or external (nasobiliary drainage)?*" And again I would like to have some comments from our panelists please.

Horst Neuhaus (Germany): I think it depends on the viscosity of the bile. So if you have pus in the biliary system, then I would not rely on an endoprosthesis because it will quickly block with the continuous cholangitis, and I would strongly recommend inserting a nasobiliary probe.

Philippus C. Bornman: Can I just ask a further question on that comment you made? Are those usually the patients with severe cholangitis? So it is the severe ones that you will not only rely on an internal stent?

Masao Tanaka (Japan): I strongly agree with Doctor Neuhaus's comment. When there is so much purulent bile, ENBD is the priority, but depending on where the stricture is and how much stone is there. When we do not know the stricture position, ENBD is better for future cholangiography. However, for confused patients or very old patients who cannot understand, they may actually pull off the catheter, so in that case a stent is better.

Sheung-Tat Fan (Hong Kong): I tend to disagree that the nasobiliary drainage is good for a patient with pus in the common bile duct. In that situation I doubt whether it could drain the part very well. So my question to Doctor Neuhaus is, have you ever really drained a bile duct with a lot of thick pus effectively by nasobili-

ary drainage? I think that in this situation we should resort to surgery as soon as possible.

Horst Neuhaus: Okay, you did not give another option to do endoscopic sphincterotomy. I think this is your next question. So if we have pus in the duct, we do sphincterotomy — we clear the duct and then we would insert a nasobiliary probe, but this was not included here in this selection.

Henry A. Pitt: Should not the size of the stent be a factor in addition? I mean, are you not limited somewhat with the naso-biliary?

Philippus C. Bornman: Yes, you use the 10-French nasobiliary, not the seven.

Joseph WY. Lau (Hong Kong): I just want to make a comment, I basically agree with Neuhaus and disagree with what S.T. Fan has said about the use of the nasobiliary catheter. I think with the trend of multiple stenting; the double pigtailed stent which I usually use is a 7-French. I think this is the space between the two stents is adequate to drain thick pus. Using I think, depending upon the pus, if it is so thick, then the addition of an endoscopic sphincterotomy would solve the issue. So in fact nowadays, in practice, I usually use a stent instead. Because, first of all, what Professor Tanaka mentioned about the accidental removal of the tube by the patient when they are confused, and also because of cutting the cost — a nasobiliary drainage is about four times more expensive than an endoscopic stent.

Chen-Guo Ker (Taiwan): In addition to the drainage effect, so we have to look at what is happening in the entire biliary duct, so therefore we have to perform a secondary, a second cholescintigraphy to look at what is happening in the entire biliary duct, so therefore ENBD is superior and first choice in my opinion.

Philippus C. Bornman: We are then going to vote on the second question, "*Which procedure do you prefer, internal (tube stent) or external (nasobiliary drainage)?*" Please vote with three options in mind, internal, external, and both.

Let us look at the Japanese consensus. Right, that is interesting. I think this is going to need some more discussion and I am not sure we can really do it now. I think we will record it and maybe we will have to refer it back to tomorrow, in terms of time, in the interests of time. But let us go on, we still have to look at the overseas consensus. Well, it looks very similar to me (refer to Fig. 2).

Addition of EST

Philippus C. Bornman: Right, we need to move on. The third question is "*For biliary drainage, not for stone removal, do you prefer addition of EST?*" and we have heard the data already, if it is a question of would you do a sphincterotomy at the time of the drainage? Yes; yes depending on the situation; and no. All right, shall we start with the voting?

Okay, that looks quite convincing, and the Japanese. . . . So there we have a no, a yes in very little. Again, I think that time is catching up on us so we will take note of that and we will take it further. It is obviously very difficult to phrase these questions because there are so many variations, but I think we are getting the message (refer to Fig. 3).

Timing of biliary drainage

Satoshi Kondo (Japan): Let us hurry to the next issue about the timing of the biliary drainage. I believe that the timing of the biliary drainage depends on severity assessment, which was discussed in the morning session. Here is the summary, but this may be partially tentative.

This is a simple question about "*The timing of biliary drainage for severe acute cholangitis.*" The options are: as soon as possible, or within 24 h, or following conservative treatment unless the patient has worsened. The results are very similar for the Japanese and overseas. Okay, we reached a consensus (refer to Fig. 4).

Satoshi Kondo: The next question is "*For moderate acute cholangitis, which is better, as soon as possible, within 24 h, or following conservative treatment unless the patient worsened?*"

This is the overseas panelists' result, it is a spilt. So we need more discussion, but we do not have enough time. Next please, the Japanese result. Again, we need more discussion tomorrow, especially about the definition of moderate acute cholangitis — that is important.

Steven Strasberg (USA): I think you might get a different result if you said within 12 h rather than within 24 h, I think it would be easier to reach a consensus.

Henry A. Pitt: And even on the first question I think the question is do you stabilize the patient first and then do the procedure, or vice-versa. And that is a better question than the question that we asked.

Jacques Belghiti (France): In acute cholangitis, I would like to know what is the best method of emergency treatment in patients with moderate cholangitis. During the last year we saw many catastrophes by the surgeons going immediately operating the patient without establishing the hemodynamics. So I am very surprised that number one and number two is in 12 h. We go immediately and do something without knowing. We know a lot of patients who improve themselves, spontaneously after antibiotic treatment. So I would like to go and have a further discussion on this point.

Thomas R. Gadacz (USA): I really disagree. This is, to me, still an emergent condition because it is very difficult to predict how these patients are going to respond. I think it is very important that we are defining acute

cholangitis as infection with obstruction. And it is important to treat both. I would no longer be comfortable with simple emergency drainage without antibiotics than I would be with antibiotics and not emergency drainage. I think you have two key components here and I think the key surgical principles are that you treat both components. You treat the infection with antibiotics and you treat the obstruction with drainage. I am really surprised that you are willing to wait to see how a patient responds and this to me is a life-threatening condition.

Jacques Belghiti: Of course it seems logical what you say. But there is one paper from France showing clearly that if you operate too quickly on the patient, you have less good results than if you operate on the patient after resuscitation, and if you go too fast to the operating room, it has catastrophic results and so that is why I would be in favor to wait during drainage. I think we can discuss this point.

Philippus C. Bornman: I think, in the interests of clarity, you are not talking about surgical drainage or surgical operation and we are talking about endoscopic drainage, so I think we need to make a clear distinction between the two.

Jacques Belghiti: Drainage for me could be the same as to operate, no, even just endoscopic, I would favor it. But I accept to be alone, do not worry.

Satoshi Kondo: Now we have changed the second option to within 12 h, so now we vote about this question. This is the overseas panelists' result; split. Next, Japanese; it is completely split. Actually, the definition of moderate acute cholangitis is unclear now, not definite. So we will discuss tomorrow morning (refer to Fig. 5a,b).

Next, we are going to vote on "*The timing of biliary drainage for mild acute cholangitis*?" This question might be complicated because, mild, the definition is not so clear. But it is almost consensus. Please, the only problem is moderate. Next, the Japanese; oh, we have reached a consensus (refer to Fig. 6).

We would like to close this session. Thank you for your cooperation.

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Journal of HBP Surgery

Need for criteria for the diagnosis and severity assessment of acute cholangitis and cholecystitis: Tokyo Guidelines

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Abstract
The Tokyo Guidelines formulate clinical guidance for healthcare providers regarding the diagnosis, severity assessment, and treatment of acute cholangitis and acute cholecystitis. The Guidelines were developed through a comprehensive literature search and selection of evidence. Recommendations were based on the strength and quality of evidence. Expert consensus opinion was used to enhance or formulate important areas where data were insufficient. A working group, composed of gastroenterologists and surgeons with expertise in biliary tract surgery, supplemented with physicians in critical care medicine, epidemiology, and laboratory medicine, was selected to formulate draft guidelines. Several other groups (including members of the Japanese Society for Abdominal Emergency Medicine, the Japan Biliary Association, and the Japanese Society of Hepato-Biliary-Pancreatic Surgery) have reviewed and revised the draft guidelines. To build a global consensus on the management of acute biliary infection, an international expert panel, representing experts in this area, was established. Between April 1 and 2, 2006, an International Consensus Meeting on acute biliary infections was held in Tokyo. A consensus was determined based on best available scientific evidence and discussion by the panel of experts. This report describes the highlights of the Tokyo International Consensus Meeting in 2006. Some important areas focused on at the meeting include proposals for internationally accepted diagnostic criteria and severity assessment for both clinical and research purposes.

Key words Evidence-based medicine · Practice guidelines · Acute cholecystitis · Acute cholangitis

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Introduction

More than 100 years have elapsed since Charcot's triad was first proposed as the characteristic findings of acute cholangitis,[1] and Murphy's sign was proposed as a diagnostic method for acute cholecystitis.[2] During this period, many new technologies have been developed for the management of acute biliary infections. Antimicrobial therapy, endoscopic techniques for both diagnosis and treatment, minimally invasive operations, including laparoscopic surgery and mini-laparotomy, and fast-track surgery[3] are good examples of such advances. Despite the great advances in medicine, acute cholangitis and acute cholecystitis are still great health problems in both developed and developing countries. According to

epidemiological studies, about 5%–15% of people in developed countries have gallstones,[4–9] and annually, 1% to 3% of these people develop severe gallstone diseases, including acute cholangitis and acute cholecystitis.[10] Although mortality related to these diseases is relatively rare, they lay a heavy burden on the public, because gallstones are so common and hospitalization is expensive. According to Kim et al.,[11] the total direct costs for gallbladder diseases per year in the United States are estimated to be $5.8 billion. Many clinical studies have been conducted to assess the risk of the disease, the accuracy of diagnostic techniques, and the effectiveness of the treatments. However, the accumulation and integration of such scientific knowledge for application to clinical practice lags behind the progress achieved in medical and surgical technology.[12] For example, many studies have suggested that there are wide variations in the care of acute biliary infections in every part of the world.[13,14] If there were "a best treatment", such variation might imply low quality of care.

In order to develop the best possible practice patterns by integrating clinical experience with the best available research information, the Committee on the Development of Guidelines for the Management of Acute Biliary Infection (principal investigator, Tadahiro Takada) (hereafter, the Committee) prepared a draft of "Evidence-based clinical practice guidelines for the management of acute cholangitis and cholecystitis". The major objectives in developing the guidelines were: (1) to propose standardized diagnostic criteria and severity assessment for both acute cholangitis and acute cholecystitis; and (2) to propose the best strategies for the management of acute biliary infections. The Committee selected a multidisciplinary Working Group composed of experts in hepatobiliary surgery, gastroenterology, intensive care, laboratory medicine, epidemiology, and pediatrics.

Through discussions within the Working Group and between the members of the scientific societies relevant to clinical practice in acute biliary infections, the draft was finalized. Subsequently, in April 2006, an international meeting was held in Tokyo to build global consensus on the management of acute biliary infection; the international consensus panel was composed of leaders in hepatobiliary medicine from across the world. In this article, we describe the methodology and process of developing of the guidelines, and the basic principles and strategies we used to reach global consensus.

Need for standardized diagnostic criteria and severity assessment

In the Guidelines, we (the Working Group) propose uniform criteria for the diagnostic criteria and severity assessment of acute cholangitis and cholecystitis. In the process of developing the Guidelines, the Committee members considered that uniform diagnostic criteria for acute biliary infections were necessary for both research and clinical purposes. Because more than a dozen different local diagnostic criteria are now in use, comparison of treatment effectiveness between studies and comparisons of clinical outcomes across institutions are often difficult. For example, although Charcot's triad (abdominal pain, fever, and jaundice) has been historically used as the diagnostic criterion of acute cholangitis, no more than 70% of patients with acute cholangitis have the triad.[15,16] The reported mortality rates of acute cholangitis have a wide range (3.9%–65%), probably due to the lack of standardized criteria. Murphy's sign has often been used in the diagnosis of acute cholecystitis. This sign is only useful when other physical findings are equivocal, as in mild cholecystitis, and it has a sensitivity and specificity of only 65% and 87%.

Management of acute biliary infections according to severity grade is also critical, because the urgency of treatment and patient outcomes differ according to the severity of the disease. A literature review revealed that terminologies used to define severe cases often failed to distinguish such cases from others. For example, Reynolds' pentad,[17] which consists of Charcot's triad plus "shock" and "decrease in level of consciousness", has been used historically to define severe acute cholangitis. The incidence of the pentad is extremely low, and is less than 10% even in severe cases.[15] There is no doubt that better criteria, which enable physicians to provide appropriate care according to the severity of the disease, are necessary.

Proposals for the diagnostic criteria were developed by beginning with existing definitions and concepts of acute biliary infections. The working group first examined how historical writings and prestigious textbooks have defined acute cholangitis and cholecystitis, and tried to propose criteria to comply with these definitions. We gave priority to the easy and early diagnosis of acute cholangitis by using noninvasive examinations. We also endeavored to incorporate the results of the latest clinical research in the diagnostic and severity assessment criteria.

By a systematic search through the literature and textbooks, the working group discussed the definitions of acute cholangitis and cholecystitis. The basic concepts of the criteria for acute cholangitis include: (1) Charcot's triad as the definite criteria for the diagnosis of acute cholangitis, and (2) the presence of "biliary infec-

tion" and "bile duct obstruction" proven by laboratory examinations and imaging. "Severe acute cholangitis" was defined as cholangitis with organ failure and/or sepsis. "Acute cholecystitis" was defined as the presentation of clinical signs such as epigastric pain, tenderness, muscle guarding, a palpable mass, Murphy's sign, and inflammatory signs. "Severe acute cholecystitis" was defined as acute cholecystitis with organ dysfunction.

Process of developing the Guidelines

We planned to use an evidence-based approach to develop our guidelines. We used established criteria and systematic methods for reviewing evidence of clinical effectiveness. However, using only evidence-based data, we were unable to establish a useful set of guidelines.[18] From the literature review, the Working Group found that, for some topics in the management of acute biliary infections, few studies could be classified at high levels of evidence, and that treatment strategies for specific health conditions sometimes differed widely by region and country. There was a concern that such lack of evidence would not produce any recommendations that would be helpful to clinicians who encountered patients with acute biliary infections. As in other areas of medicine, we recognized that, if the authors of the Tokyo Guidelines insisted upon strict adherence to an approach which accepted only studies rated at a high level of evidence in order to formulate guidelines, the vast majority of medical practice would be excluded from the practice guidelines. Therefore, to develop the Guidelines, we shifted our approach to one which combined the best of the literature studies with the best clinical opinion, based on a formal consensus approach. This strategy has the dual advantage of allowing the formulation of the best guidelines possible at the present time, while pointing out areas in which studies are needed in order to formulate future guidelines based solely upon high levels of evidence.

Between April 1 and 2, 2006, an International Consensus Meeting on Acute Biliary Infections was held in Tokyo, in which an expert panel consisting of 30 overseas panelists and 30 Japanese panelists tried to reach consensus on recommendations at a structured 2-day conference. The expert panel was provided with the draft of the guidelines prepared by the Working Group that reviewed the existing scientific evidence for a procedure, as well as providing a list of indications for performing the procedure. In principle, the recommendations were based on the best available evidence. However, in the absence of high-quality evidence, expert consensus was integral to developing the Guidelines. The Guidelines are based on evidence, on discussion by the experts, and on consensus reached by voting. The panel recognized that specific patient care decisions may be at variance with these guidelines and that these decisions are the prerogative of the patient and of the health professionals providing care.

The Guidelines are intended not only for specialists engaged in the diagnosis and treatment of acute biliary diseases but also for the general practitioner who has first contact with these patients. The Guidelines were prepared to provide medical workers who play an active part at the front line with the best medical practice employing currently available data for the best outcome of the latest clinical research. The Guidelines consist of "clinical questions" that clinicians have in their daily medical practice, and responses to them. For a better understanding of the Guidelines, the sequences of diagnosis and treatment are explained with flowcharts. It is our goal for the Guidelines to help users to provide best medical practice according to their specialty and capability, and thereby to improve the management of acute biliary infection.

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Techniques of biliary drainage for acute cholangitis: Tokyo Guidelines

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Abstract
Biliary decompression and drainage done in a timely manner is the cornerstone of acute cholangitis treatment. The mortality rate of acute cholangitis was extremely high when no interventional procedures, other than open drainage, were available. At present, endoscopic drainage is the procedure of first choice, in view of its safety and effectiveness. In patients with severe (grade III) disease, defined according to the severity assessment criteria in the Guidelines, biliary drainage should be done promptly with respiration management, while patients with moderate (grade II) disease also need to undergo drainage promptly with close monitoring of their responses to the primary care. For endoscopic drainage, endoscopic nasobiliary drainage (ENBD) or stent placement procedures are performed. Randomized controlled trials (RCTs) have reported no difference in the drainage effect of these two procedures, but case-series studies have indicated the frequent occurrence of hemorrhage associated with endoscopic sphincterotomy (EST), and complications such as pancreatitis. Although the usefulness of percutaneous transhepatic drainage is supported by the case-series studies, its lower success rate and higher complication rates makes it a second-option procedure.

Key words Cholangitis · Endoscopic sphincterotomy · Biliary drainage · Percutaneous · Endoscopy · Endoscopic cholangiopancreatography · Guidelines

Introduction

Acute cholangitis may progress rapidly to a severe form, particularly in the elderly, and the severe form often results in a high mortality (level 4).[1–3] When Reynolds and Dargan[1] published their report, surgical operation was the only available treatment, and the mortality rate was steep. Even now, when the mortality rate has declined, due to the ubiquitous application of endoscopic and percutaneous transhepatic biliary drainage, acute cholangitis can be fatal unless it is treated in a timely way. Although endoscopic drainage is less invasive than other drainage techniques and should be considered as the drainage technique of first choice (level 2b),[4] details of its procedures remain controversial. This article outlines various biliary drainage techniques, especially in regard to endoscopic procedures.

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Fig. 1a,b. Pull-type sphincterotome. **a** A pull-type sphincterotome is shown; it has various applications, and is useful for opening the bile duct. **b** The direction of the tip of the blade can be manipulated by pulling. The direction can usually be changed by using a guidewire

Fig. 2. Push-type sphincterotome. The direction of the blade cannot be altered, but its length and form can be changed. It can be used for precutting

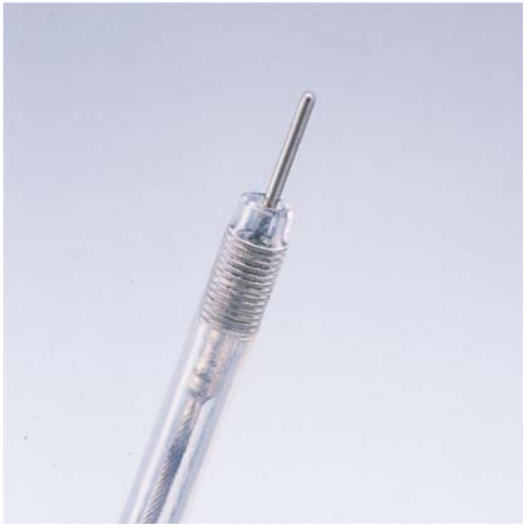


Fig. 3. Needle-type sphincterotome. Because of the needle point, opening of the bile duct can be performed

Techniques of endoscopic biliary drainage

Transpapillary biliary drainage for acute cholangitis is based on selective cannulation into the bile duct with endoscopic retrograde cholangiopancreatography (ERCP). However, as these drainage procedures are different in regard to: (i) the additional application of endoscopic sphincterotomy (EST), and (ii) the selection of either endoscopic nasobiliary drainage (ENBD) or stent placement, they are explained below in detail.

ERCP

ERCP is a procedure to insert a contrast test catheter into the papilla, using a duodenal scope to visualize the bile duct. To secure a drainage route (for ENBD or stent placement), successful selective cannulation into the bile duct is essential. If cannulation deep into the bile duct is difficult, replacement of the catheter, the use of a guidewire, and precutting (by EST, explained below), are necessary. If the cannulation into the bile duct fails, other drainage, such as percutaneous transhepatic biliary drainage, is necessary. Also, the quantity of con-

trast medium should be minimized to avoid the infusion of an excessive amount, which may exacerbate the cholangitis.

EST

Standard techniques

EST is a procedure used widely not only in the treatment of choledocholithiasis but also as a drainage procedure for malignant biliary obstruction. Sphincterotomes used for incision include several types such as: the pull-type (Fig. 1a,b), push-type (Fig. 2), needle type (Fig. 3) and, the shark's fin-type, and others, each of which has a different length of exposed wire and different tip shape. The most common sphincterotome is the pull type. The pull-type sphincterotome is useful when ERCP is difficult, because the direction of the tip of the sphincterotome can be changed by adjusting the tension of the blade (Fig. 1b). The push-type and needle-type are used for difficult cases.

A common EST technique is to perform a high-frequency electric surgical incision of the duodenal papilla, using a sphincterotome selectively cannulated in the bile duct (Figs. 4 and 5). In EST for drainage purposes, unlike that for stone removal, only a limited incision is necessary (level 4).[5] Acute pancreatitis and cholangitis are common complications caused by EST, and the incidence of acute pancreatitis, known to become fatal once it progresses severely, depends on the skills of the endoscopist (level 1b, level 4)[6,7] (Table 1).

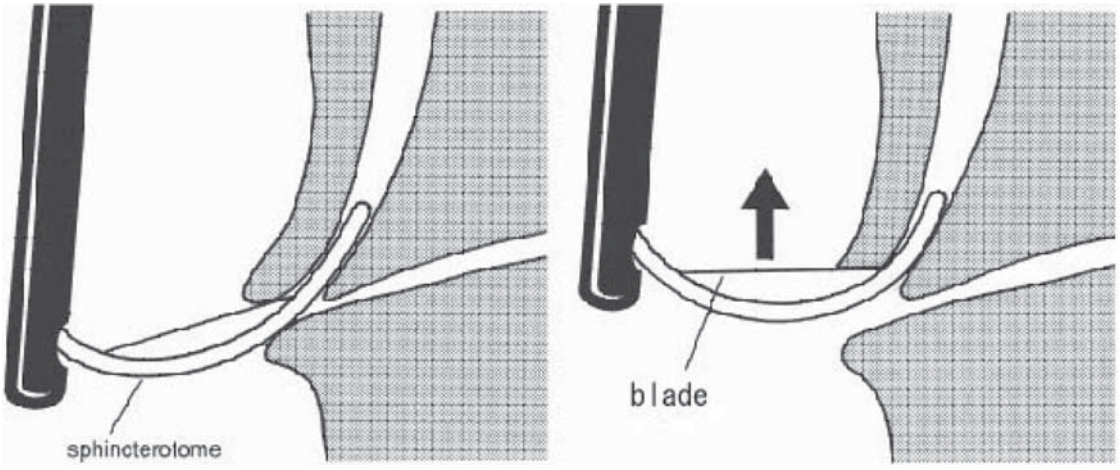
Precutting techniques

Precutting is an incision of the papilla to facilitate cannulation into the bile duct when selective cannulation is impossible. EST can be completed by a common procedure after selective cannulation into the bile duct becomes possible. The method using a needle-type sphincterotome for probing in the opening of the bile duct is common (Fig. 6), but there is also a method to incise the tips of the bile duct with a push-type or shark's fin-type sphincterotome. The types of sphincterotome and the detailed procedures used differ depending on the medical institution. It is also known that precutting is likely to cause serious complications such as acute pancreatitis and perforation, and therefore it can be used only by skilled endoscopic surgeons (level 1b, level 4).[6,7]

Significance of EST in endoscopic biliary drainage

According to some case-series studies, the reasons that additional EST are not necessary in acute cholangitis are that:

(i) The application of additional EST to drainage produces no difference in effect

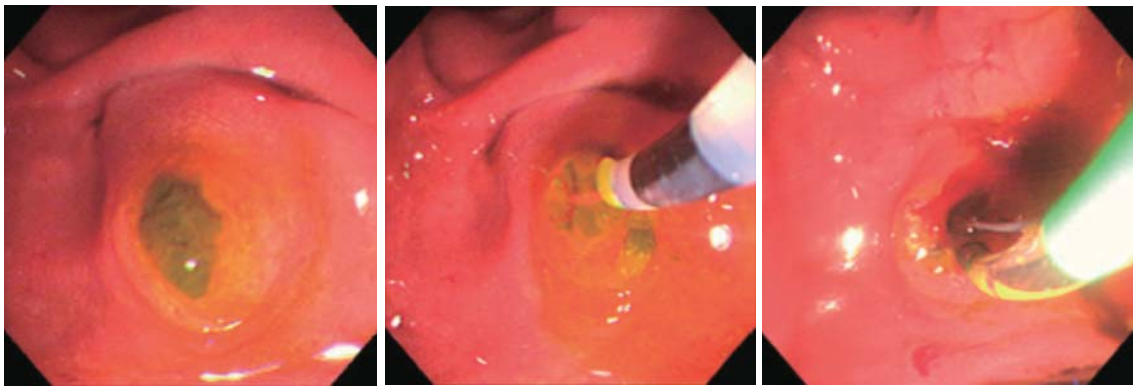


a b

Fig. 4a,b. Standard techniques for endoscopic sphincterotomy (EST). **a** Selective cannulation of the bile duct. **b** A high-frequency electric surgical incision of the papilla of Vater is made with the blade

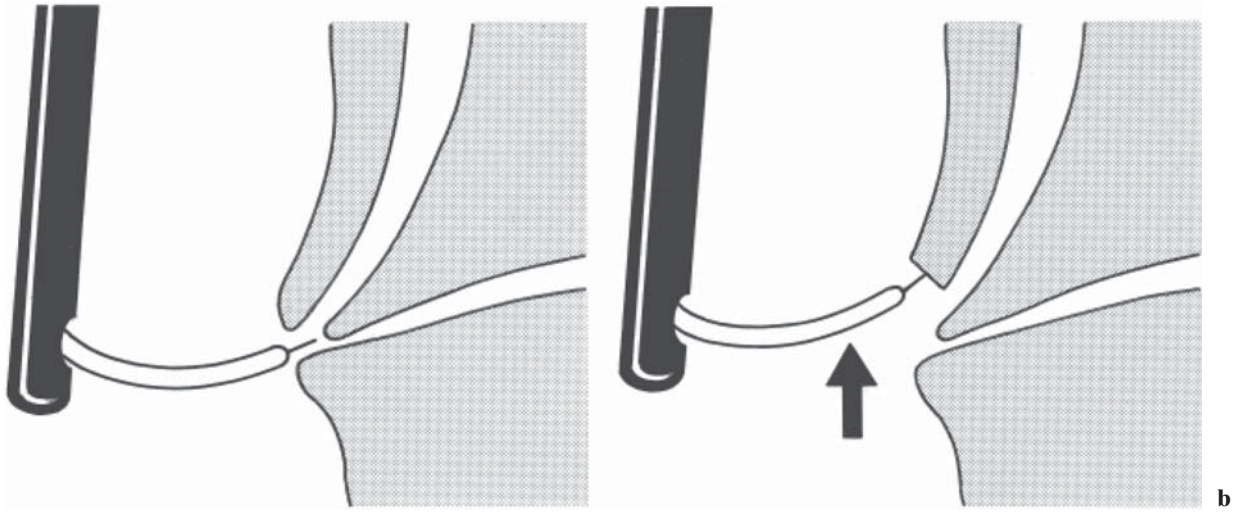
Table 1. Complications caused by EST

Author	*n*	Pancreatitis	Hemorrhage	Cholangitis	Cholecystitis	Perforation	Mortality
Freeman (1996)[6]	2347	5.4%	2.0%	1.0%	0.5%	0.3%	0.4%
Cotton (1991)[7]	7729	1.9%	3.0%	1.7%		1.0%	1.3%



a b,c

Fig. 5a–c. Example of EST procedure. **a** Gallstones are visible via the duodenal papilla. **b** In this patient, cannulation with an endoscopic catheter resulted in resolution of the debris-like stones. **c** The catheter was replaced by a high-frequency electric sphincterotome



a b

Fig. 6a,b. Precutting EST techniques with a needle-type sphincterotome. **a** Needle-knife sphincterotomy was performed, starting from the papillary orifice, cutting upward. **b** Incising through the wall of the major papilla is performed with the needle-knife until achieving access into the bile duct

(ii) the additional EST causes complications such as hemorrhage.

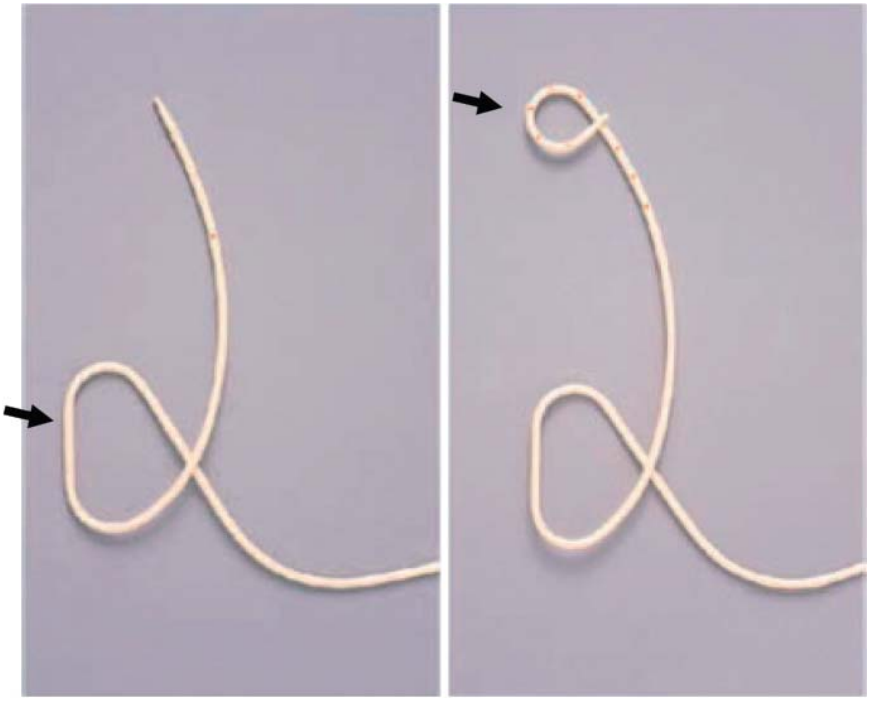
Acute cholangitis is one of the risk factors for post-EST hemorrhage (level 1b),[6] and the use of EST in patients with severe (grade III) disease complicated by coagulopathy should be avoided. On the other hand, EST has advantages such as:

(a) Not only drainage but also single-stage lithotomy can be employed in patients with choledocholithiasis (not complicated by severe cholangitis)
(b) Precutting can ensure a drainage route into the bile duct in patients in whom selective cannulation is difficult.

Endoscopic drainage employed for acute cholangitis does not always require EST (level 4).[8,9] However, precutting may be indispensable in performing drainage in some patients with impacted stones in the papilla of Vater, and whether or not additional EST should be conducted depends on the condition of the patient and the skills of the endoscopist. In the Guidelines, readers are reminded to be cautious when additional EST is employed.

Endoscopic biliary drainage (EBD)

Endoscopic drainage includes not only endoscopic biliary drainage (EBD) but also EST without stent



a **b**

Fig. 7a,b. Endoscopic nasobiliary drainage (ENBD) tubes. **a** Straight-tip tube. The leading portion of the tube is straight. A "duodenal loop" of the tube (*arrow*) is formed to prevent dislocation. **b** Pigtail-tip tube (*arrow*). To prevent dislodgement, the leading portion of the tube has a "pigtail"

insertion, which means that calculus removal can be performed with only one endoscopic procedure. EBD is of two types endoscopic nasobiliary drainage (ENBD; external drainage) and stent placement (internal drainage). No difference between these two methods was proven by past RCTs (level 2b),[10,11] and the Guidelines suggest that either drainage procedure may be chosen. Internal drainage does, however, confer less electrolyte disturbance as there is no external loss of bile and its contents.

Endoscopic nasobiliary drainage (ENBD)

ENBD is an external drainage procedure done by placing a 5- to 7-Fr tube, using a guidewire technique, after selective cannulation into the bile duct, and it is used to complete nasobiliary drainage (Fig. 7–10). ENBD has these advantages:

(i) No additional EST is required
(ii) Clogging in the tube (external drain) can be washed out
(iii) Bile cultures can be done

However, because of the patient's discomfort from the transnasal tube placement, self-extraction and dislocation of the tube are likely to occur, especially in elderly patients. Loss of electrolytes and fluid as well as collapse of tubes by twisting, may also occur.

Additional EST must be considered for the removal of concomitant bile duct stones and viscous bile or pus in patients with suppurative cholangitis.

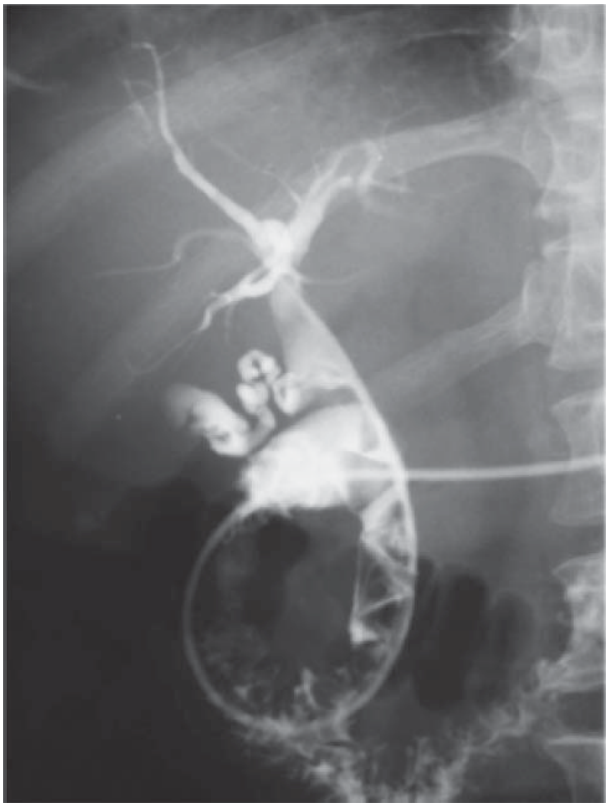


Fig. 8. Cholangiography through ENBD tube. Many stones are seen in the bile duct. Attention should be paid: cholangiography should be performed after improvement of inflammation

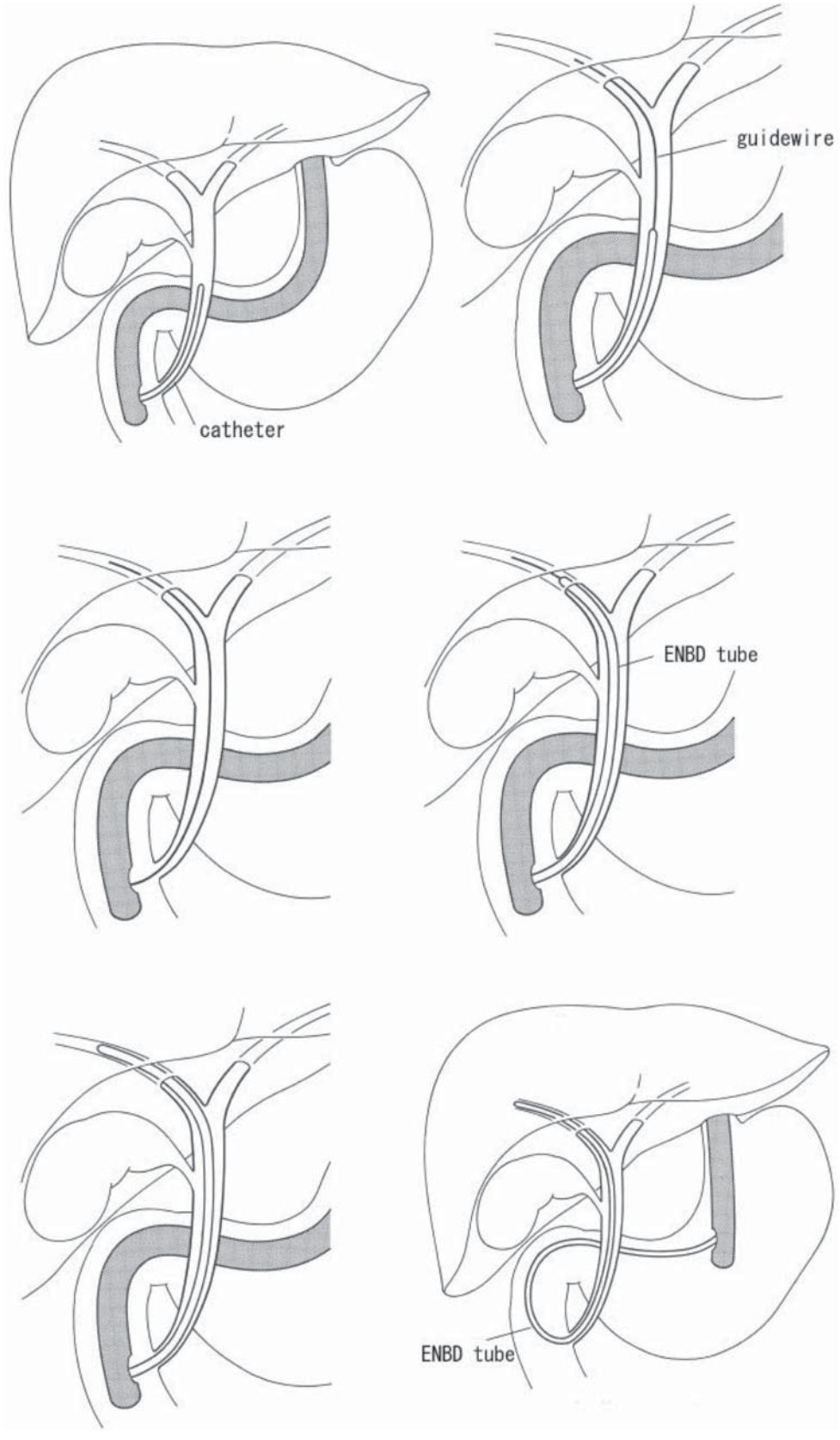


Fig. 9a–f. ENBD procedure: part 1. **a** An endoscopic catheter is cannulated into the bile duct. **b** A guidewire is passed through the catheter into the bile duct. **c** The catheter is withdrawn. **d** The ENBD tube is passed along the guidewire. **e** The guidewire is withdrawn. **f** The endoscope is removed while applying pushing pressure on the ENBD tube to keep it in place

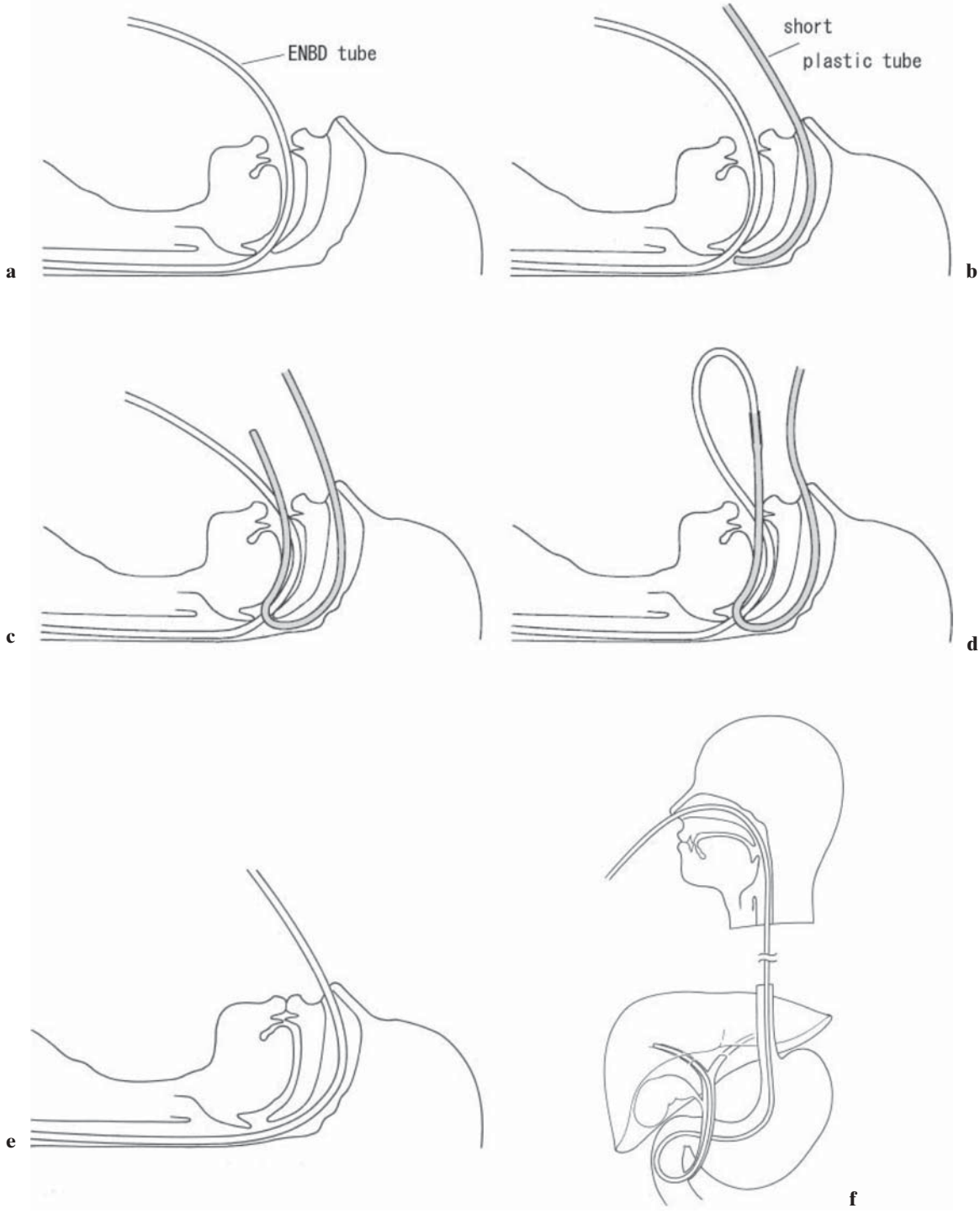


Fig. 10a–f. ENBD procedure: part 2. **a** The ENBD tube is inserted transorally. **b** A short plastic tube is inserted transnasally in order to engage the ENBD tube. **c** Surgical forceps are used to pull the leading end of the short plastic tube out orally. **d** The tubes are connected by inserting the end of the ENBD tube into the short plastic tube. **e** The short plastic tube and the connected ENBD tube are then pulled back out nasally. **f** A 5- to 7-French tube is used for biliary drainage via the nasal route

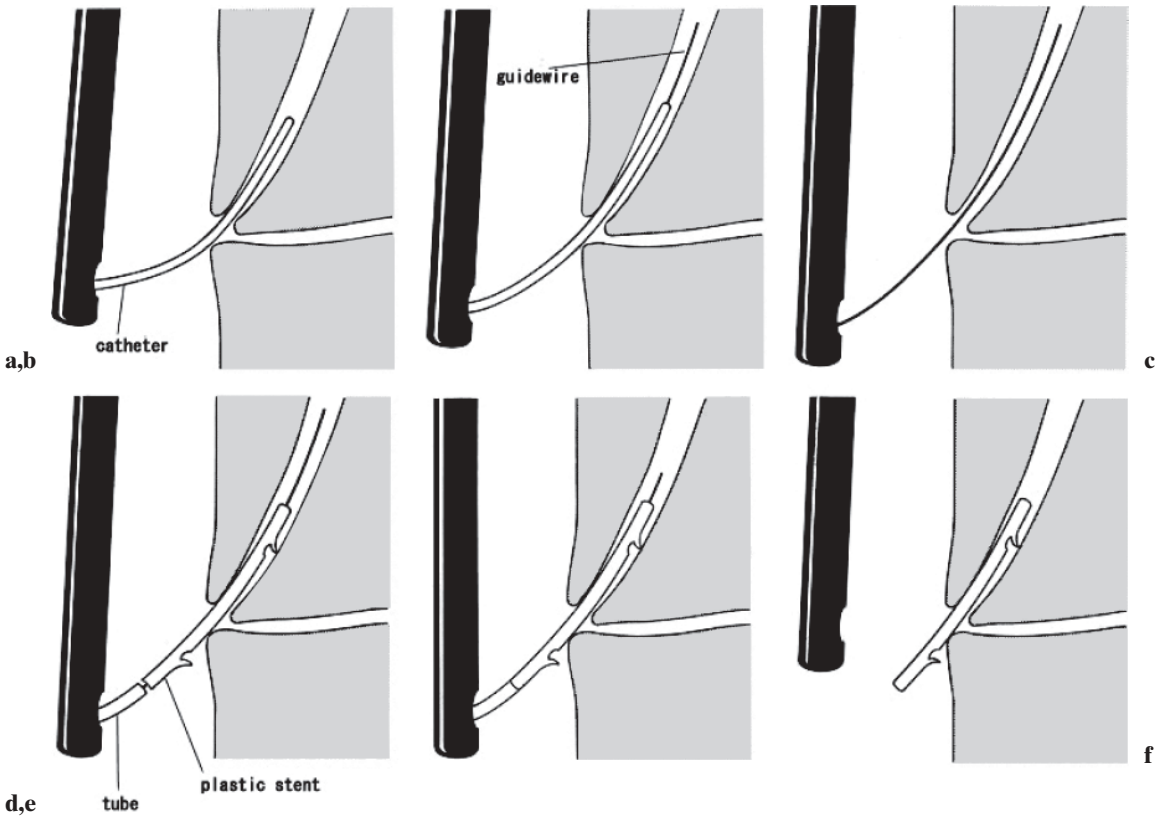


Fig. 11a–f. Plastic stent placement (7-Fr straight plastic stent). **a** An endoscopic catheter is cannulated into the bile duct. **b** A guidewire is passed through the catheter into the bile duct. **c** The catheter is withdrawn. **d** A plastic stent is inserted along the guidewire into the bile duct by using a pusher tube. **e** The guidewire is removed while pushing on the pusher tube (care should be taken not to deviate from the bile duct). **f** The endoscope is removed, leaving the plastic stent in place

Plastic stent placement

Plastic stent placement is an internal drainage procedure done to place a 7- to 10-Fr plastic stent in the bile duct, using a guidewire after selective cannulation into the bile duct (Figs. 11 and 12). There are two different stent shapes, a straight type with flaps on both sides, and a pig tail type, to prevent dislocation (Fig. 13). Absence of discomfort and no loss of electrolytes or fluid relative to transnasal biliary drainage are advantages. However, as it cannot be known in real time whether the stent is patent, there is a risk of dislodgement or clogging of the stent. The other disadvantage is that when a stent with a diameter larger than 7-Fr is inserted, EST is necessary.

EST without stent insertion

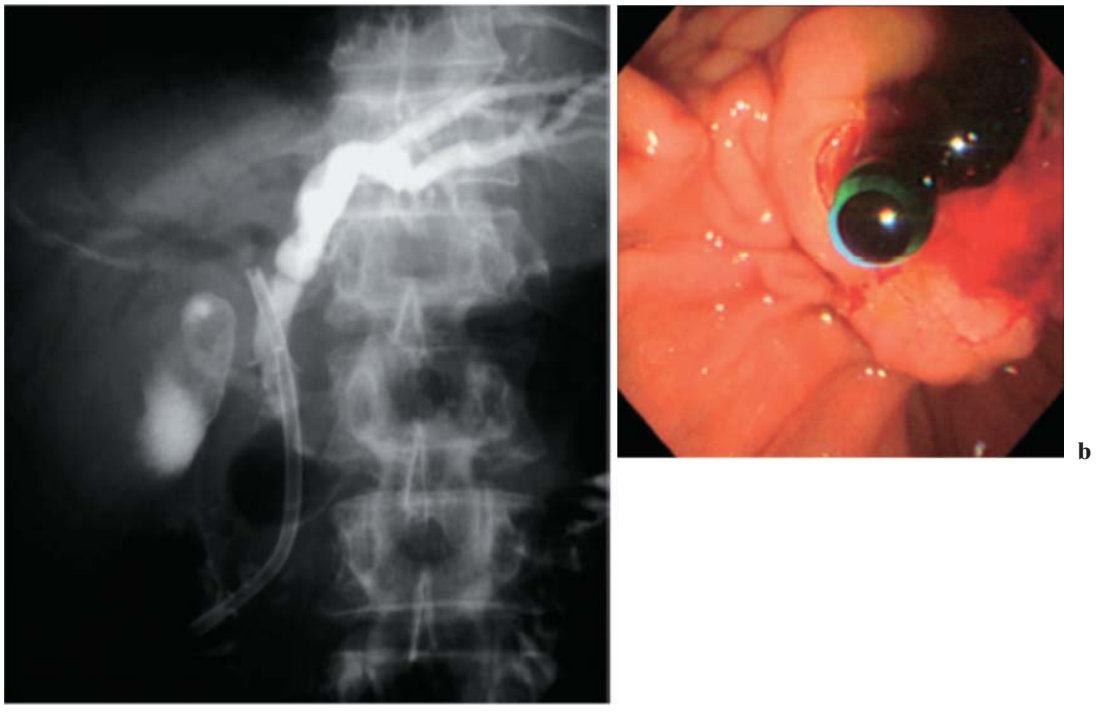
EST without stent insertion can be used to remove bile duct calculi as well as for drainage. This method can shorten the hospital stay because both calculus removal and drainage are completed with only one endoscopic procedure. However, caution should be exercised, with monitoring for cholangitis due to residual calculi or sludge.

Table 2. Serious complications caused by PTCD[12]

Complication	Rate
Sepsis	2.5%
Hemorrhage	2.5%
Localized inflammation/infection (abscess, peritonitis, cholecystitis, pancreatitis)	1.2%
Pleural effusion	0.5%
Death	1.7%

Techniques of percutaneous transhepatic cholangial drainage (PTCD)

Though there are no studies comparing percutaneous transhepatic cholangial drainage PTCD; also known as percutaneous transhepatic biliary drainage; PTBD, and endoscopic drainage, PTCD should applied, in principle, to those patients who cannot undergo endoscopic drainage because of the possible serious complications of PTCD, including intraperitoneal hemorrhage and biliary peritonitis (level 4) (Table 2[12]) and a long hospital stay. A propensity for hemorrhage is a relative contraindication, but if there is no other lifesaving method,



a b

Fig. 12a,b. Leaving the stent in place (acute cholangitis, arising from chronic pancreatitis caused by bile duct stricture). **a** Endoscopic cholangiography (ERC) shows the stent in place. **b** Endoscopic view immediately following stent placement. Bile flows to the duodenum via the stent

a b

Fig. 13a,b. Types of plastic stent. **a** Straight stent : the stent has two flaps to prevent dislocation or deviation. Should EST be required, a 10-Fr or larger stent can be used. **b** Pigtail stent: both ends of the stent have a "pigtail" form to prevent dislocation or deviation. Maximum stent size is 7 Fr

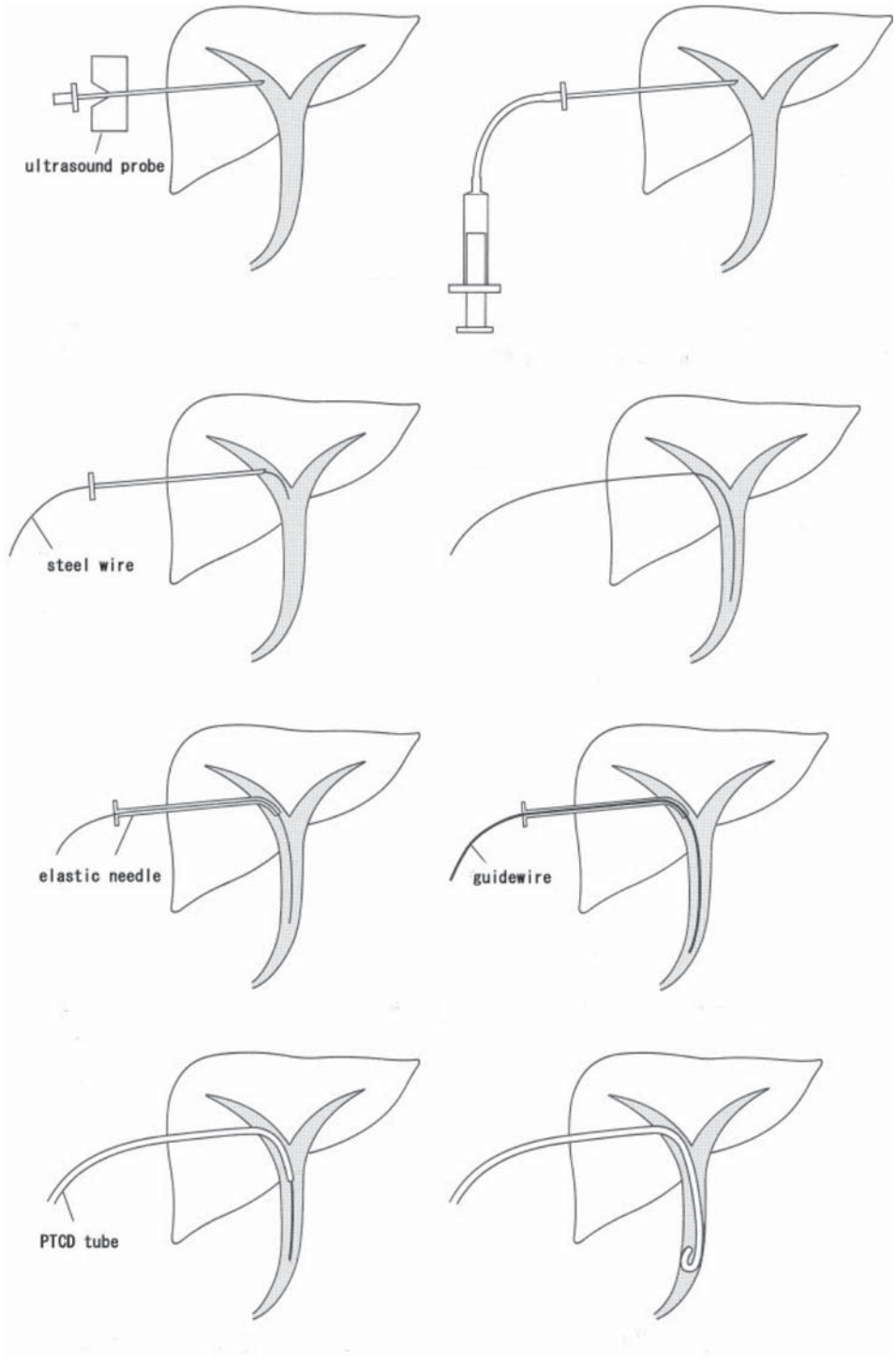


Fig. 14a–h. Percutaneous transhepatic cholangial drainage (*PTCD* or PTBD [biliary]) procedure. **a** Under ultrasound guidance, the intrahepatic bile duct is punctured by the use of a hollow needle (external cylinder with a mandolin). **b** Only the mandolin is removed, and the cylinder remains. After confirming the backflow of bile, bile duct imaging is performed. **c** A steel wire is inserted through the cylinder. **d** After confirming sufficient insertion of the wire into the bile duct, the hollow needle (cylinder with the mandolin) is removed. **e** An elastic needle is passed over the wire. **f** Backflow of bile is confirmed after withdrawing the inner tube from the elastic needle. A guidewire is then inserted. **g** A PTCD (or PTBD) tube is passed over the guidewire. **h** The guidewire is withdrawn and the tube is left and fixed in place

PTCD is indicated. In view of this, the Guidelines give recommendation grades A and B to endoscopic drainage and PTCD, respectively.

Before the widespread application of ultrasonography, a procedure to puncture the bile duct under fluoroscopic control following PCTD (level 4)[13] was employed. But because it caused complications in many cases, puncture under ultrasonography is more common now (level 4).[14]

After ultrasound-guided transhepatic puncture of the intrahepatic bile duct is done with an 18- to 22-G needle to confirm backflow of bile, a 7- to 10-Fr catheter is placed in the bile duct under fluoroscopic control, using a guidewire (Seldinger technique). As a guidewire

cannot be inserted directly when a 22-G needle is used, it is necessary to insert the guide-wire after dilating the bile duct with an elastic needle, using a steel wire. This procedure, requiring another step, is a little complicated (see Fig. 14), but puncture with a small-gauge (22-G) needle is safer in those patients without biliary dilatation. According to the Quality Improvement Guidelines produced by American radiologists, the success rates of drainage are 95% in patients with biliary dilatation and 70% in those without biliary dilatation (level 4).[13]

Techniques of open drainage

Patients with acute cholangitis are preferentially treated with a noninvasive drainage procedure such as endoscopic drainage and PTCD, and only a few undergo open drainage. However, open drainage may be indicated for patients who cannot undergo such noninvasive drainage procedures, for anatomical and structural reasons, including patients after Roux-en-Y choledochojejunostomy with a propensity for hemorrhage. In open drainage, the goal is to decompress the biliary system. Simple procedures such as T-tube placement without choledocholithotomy should be recommended, because prolonged operations should be avoided in such ill patients (level 4).[15]

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Journal of HBP Surgery

Techniques of biliary drainage for acute cholecystitis: Tokyo Guidelines

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Abstract
The principal management of acute cholecystitis is early cholecystectomy. However, percutaneous transhepatic gallbladder drainage (PTGBD) may be preferable for patients with moderate (grade II) or severe (grade III) acute cholecystitis. For patients with moderate (grade II) disease, PTGBD should be applied only when they do not respond to conservative treatment. For patients with severe (grade III) disease, PTGBD is recommended with intensive care. Percutaneous transhepatic gallbladder aspiration (PTGBA) is a simple alternative drainage method with fewer complications; however, its clinical usefulness has been shown only by case-series studies. To clarify the clinical value of these drainage methods, proper randomized trials should be done. This article describes techniques of drainage for acute cholecystitis.

Key words Acute cholecystitis · Cholecystostomy · Drainage · Percutaneous · Endoscopy · Acalculous cholecystitis · Guidelines

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Introduction

Biliary drainage used to be a surgical procedure consisting of external biliary drainage done under local anesthesia — called "percutaneous cholecystostomy". With the popularization of ultrasonography, percutaneous transhepatic gallbladder drainage (PTGBD), which is an interventional procedure, has become a standard method. The usefulness of PTGBD as a drainage method for high-risk patients is endorsed by many case-series studies (level 4),[1–8] but its superiority over conventional treatment has not been proven by randomized controlled trials (RCTs) based on the highest level of evidence (level 2b).[11] Percutaneous transhepatic gallbladder aspiration (PTGBA), is an alternative biliary drainage method in which the gallbladder contents are puncture-aspirated without placing a drainage catheter. The usefulness of PTGBA has been reported only in case-series studies (level 4).[3,9,10]

Acalculous cholecystitis is known to occur in elderly or high-risk patients with poor systemic condition, and it can be treated by biliary drainage alone (level 4).[1,2,13,14]

This article describes the details of drainage procedures used for acute cholecystitis, and indicates the grades of recommendation for the procedures established by the Guidelines.

Procedures for gallbladder drainage

Percutaneous transhepatic gallbladder drainage (PTGBD)

PTGBD is an essential technique for nonoperative gallbladder drainage. After ultrasound-guided transhepatic gallbladder puncture is done 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). The advantage of the technique is its simplicity. However, although bile aspiration and lavage are easily performed by this technique, it has disadvantages in that the drainage tube cannot be extracted until a fistula forms around the tube (around 2 weeks) and there is a risk of dislocation of the tube. The superiority of PTGBD over conservative treatment has not be proven by RCTs (level 2b)[9] (Table 1).

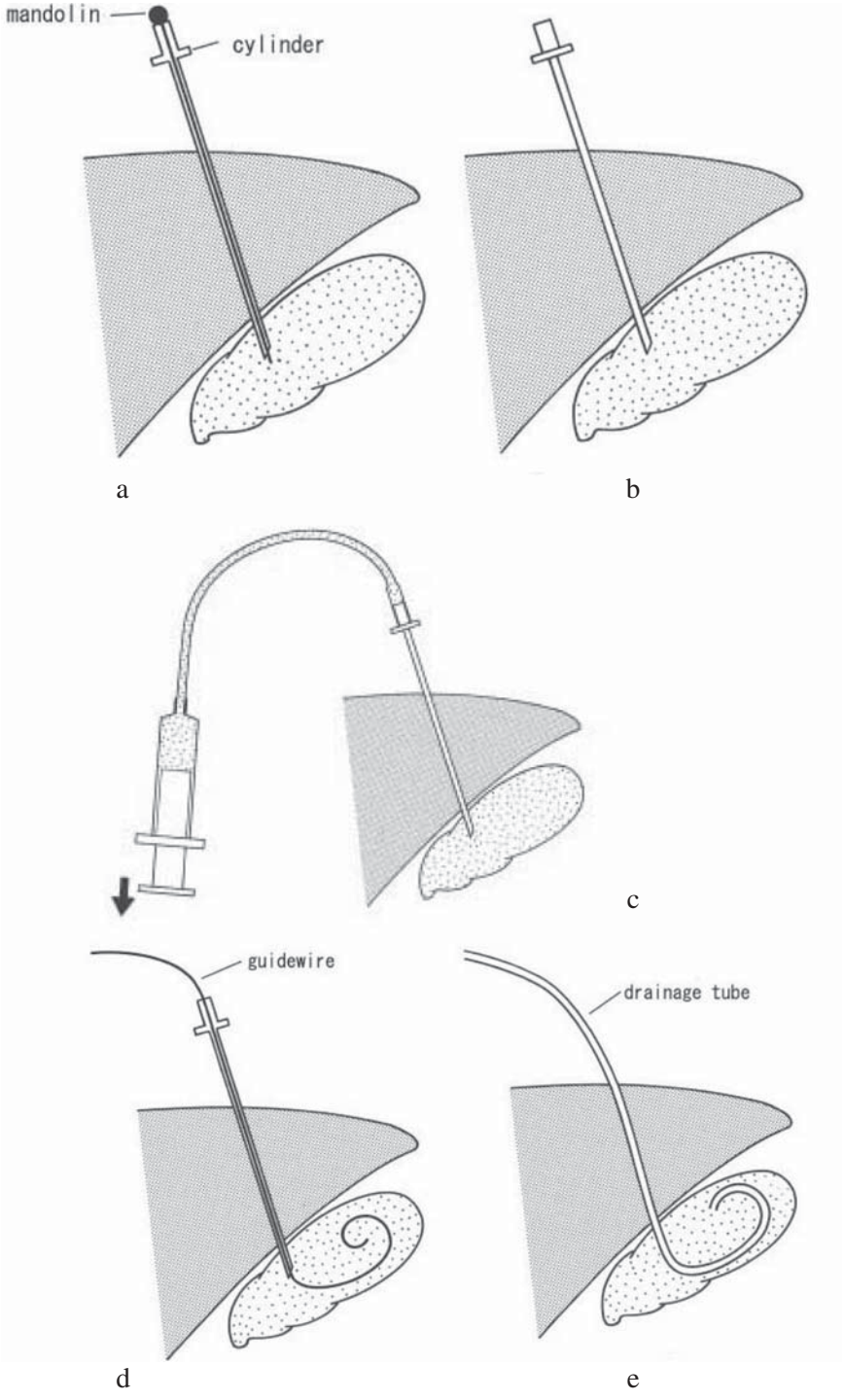

Fig. 1a–e. Percutaneous transhepatic gallbladder drainage (PTGBD) procedure. **a** A hollow needle (external cylinder with a mandolin) is inserted into the gallbladder. **b** Only the mandolin is removed and the external cylinder remains. **c** Backflow of bile is confirmed. **d** A guidewire is inserted into the gallbladder. **e** After removal of the external cylinder, a drainage tube is passed over the guidewire into the gallbladder. The guidewire is then withdrawn, and the tube is fixed to the skin

Table 1. RCT comparing PTGBD and conservative treatment for high-risk acute cholecystitis (PTGBD)

	n	(ICU[a])	Symptom improvement	Mortality	
PTGBD group	63	(6)	86%	17.5%	
Conservative treatment	60	(2)	87%	13%	NS

[a]No. of patients in ICU (intensive care unit)
(Adapted from reference 9)

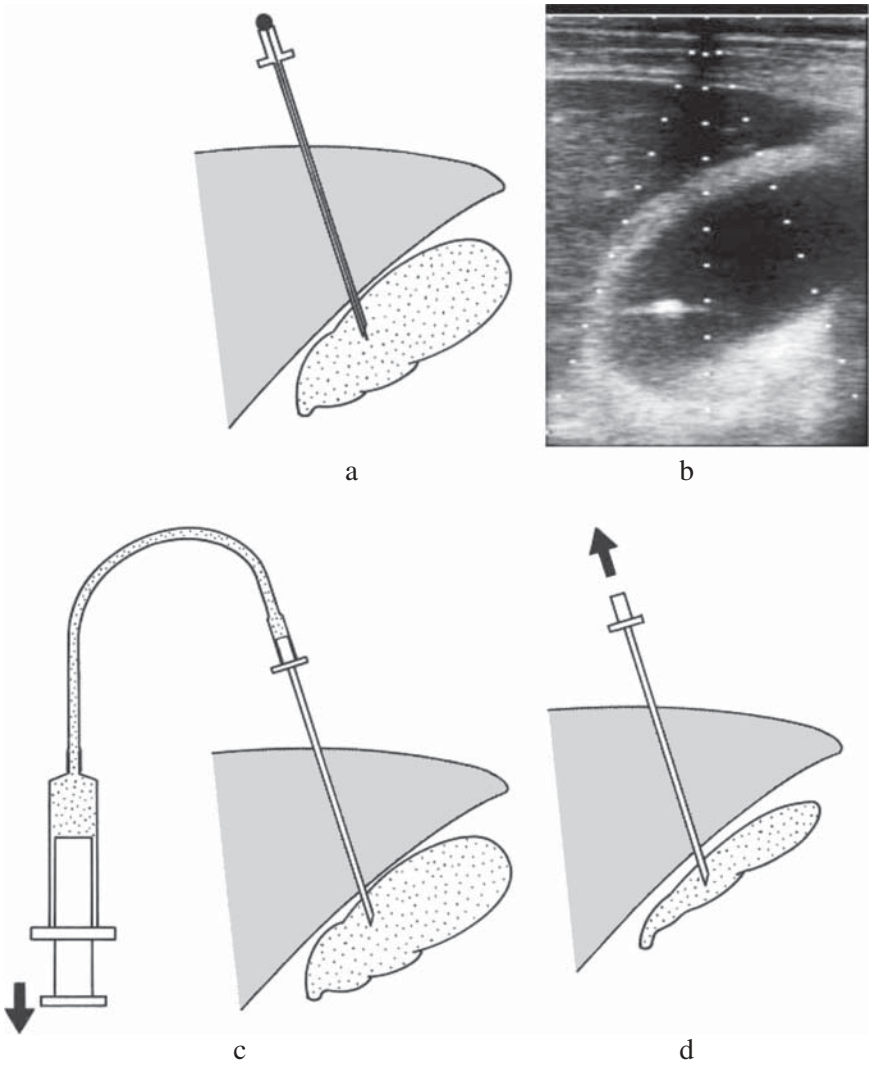

Fig. 2a–d. Percutaneous transhepatic gallbladder aspiration (PTGBA) procedure. **a** Under ultrasound guidance, the gallbladder is punctured transhepatically by a needle with a mandolin. The mandolin is then removed. **b** Real-time ultrasound image: the needle tip is confirmed as a high-echoic spot in the gallbladder, revealing successful puncture under real-time ultrasound guidance. **c** The mandolin is removed, and bile is aspirated. **d** After sufficient aspiration of bile, the needle is withdrawn

Percutaneous transhepatic gallbladder aspiration (PTGBA)

PTGBA is a method to aspirate bile via the gallbladder with a small-gauge needle under ultra sonographic guidance (Fig. 2); it is an easy low-cost bedside-applicable procedure, without X-ray guidance. It has various advantages as compared with PTGBD, such as the absence of complications, including those caused by tube displacement, as it requires no drainage tube management[3] and less restriction of the patient's activity of daily living (ADL), but an RCT (level 2b)[12] has indicated that the drainage is less effective (Table 2). However, as it is known that the effect of drainage is enhanced when PTGBA is performed two times or more (level 4),[10,11] an RCT should be performed to confirm the effect of PTGBA by comparing it with PTGBD not only in terms of drainage but also in terms of other outcomes, including complications and the effects on patients' ADL.

Table 2. Comparisons of results for PTGBA and PTGBD

Authors	Number of patients	Technical success	Clinical responses	Complications
Ito (2004)[12]	PTGBA, 28	82%	61%	0.4%
	PTGBD, 30	100%	90%*	0.3%
Kutsumi (2004)[10]	PTGBA, 94	100%	83% (91%[a])	1.1%
	PTGBD, 13	100%	—	23.1%
Chopra (2001)[3]	PTGBA, 31	97%	74%	0
	PTGBD, 22	97%	86%	12%*
Mizumoto (1992)[11]	PTGBA, 58	98%	81% (94%[a])	2.5%
	—			

* $P < 0.05$
[a] PTGBA was performed twice or more

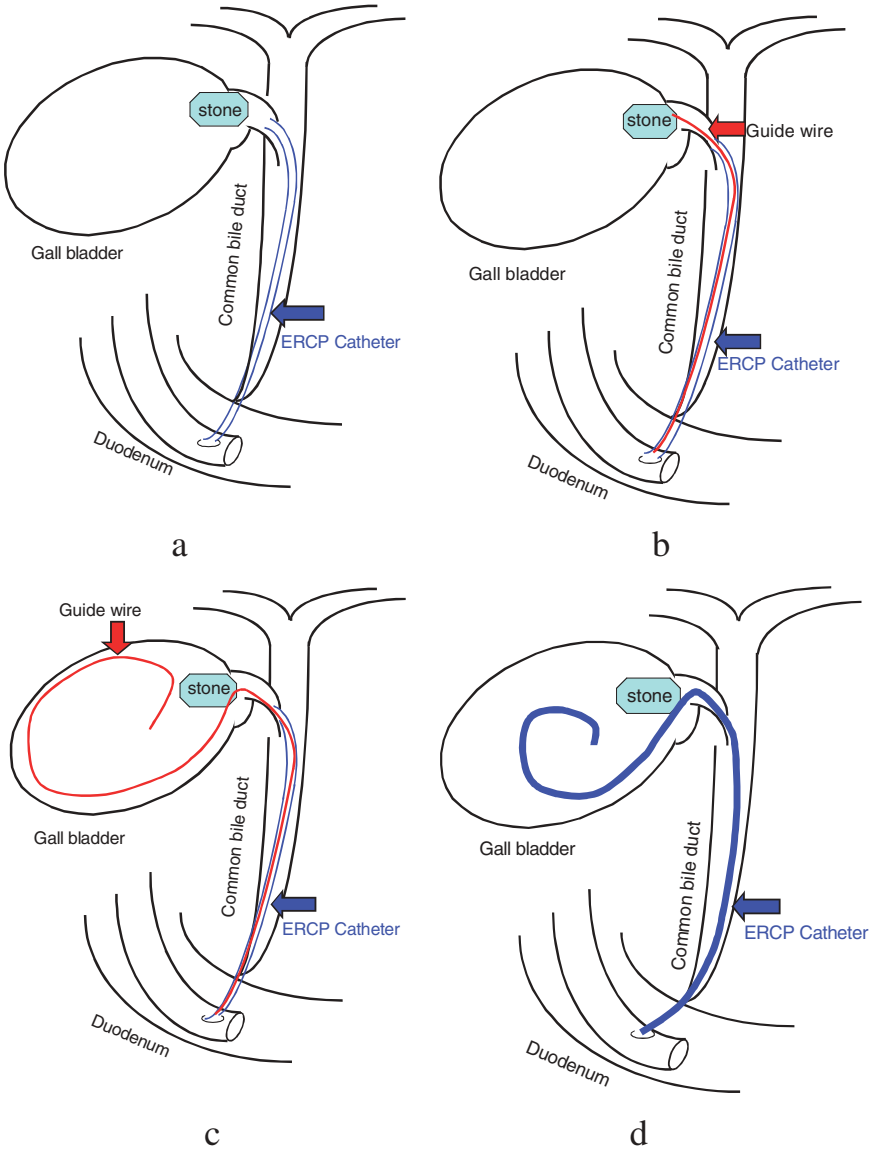

Fig. 3a–d. Endoscopic nasogallbladder drainage (ENGBD) procedure.[19] **a** An endoscopic retrograde cholanglopancreatography (*ERCP*) catheter was inserted in the cystic duct, but the gallbladder was not visualized because of a stone impacted in the neck of the gallbladder. **b** Through the ERCP catheter, a hydrophilic guidewire was passed beyond the obstruction. **c** A radiofocus guidewire was inserted into the gallbladder. **d** An ENGBD catheter was inserted into the gallbladder for drainage

For PTGBA, considering the potential for bile leakage into the peritoneal cavity, a transhepatic puncture route is chosen, and the gallbladder contents should be completely aspirated until the gallbladder collapses, as shown by ultrasound-guided checking of the needle tip (Fig. 2).

The use of a large-gauge (18-G) needle is convenient for aspirating highly viscous bile containing inflammatory products and biliary sludge, but we should be careful to prevent bile leakage after removing the needle. While 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. Many stadies (level 2b, 4)[10–12] report the use of 21-G needles.

Endoscopic nasogallbladder drainage (ENGBD)

ENGBD is an external drainage procedure done by placing a 5- to 7-Fr tube, using a guide-wire technique, after selective cannulation into the gallbladder (Fig. 3). ENGBD can be used for patients with severe comorbid conditions, especially those with end-stage liver disease, in whom the percutaneous approach is difficult to perform. However, because it requires a difficult endoscopic technique, and relevant case-series studies have been conducted only at a limited number of institutions (level 4),[15–19] ENGBD has not been established as a standard method.

The Guidelines established the following grades of recommendation for gallbladder drainage, based on the currently available evidence.

Q1. What procedure should be chosen when gallbladder drainage is required in acute cholecystitis?

PTGBD: Recommendation
PTGBA: Recommendation
ENGBD: Recommendation

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Discussion at the Tokyo International Consensus Meeting

PTGBD versus conservative treatment

Henry Pitt (USA): This area is an area that is obviously controversial and would be a great opportunity to do a randomized trial, a proper randomized trial of preoperative drainage followed by surgery versus surgery alone, and that is the trial that needs to be done.

Horst Neuhaus (Germany): Yes, I agree, if you consider the comment from Doctor Strasberg this morning (present state of laparoscopic cholecystectomy in America), you mentioned that in severe acute cholecystitis the incidence of complications is higher in early cholecystectomy, and therefore I also think it would be worthwhile to set up a randomized trial in these selected groups of severe acute cholecystitis.

Steven Strasberg (USA): I think an important point is when the percutaneous drainage is done. So if a patient has moderate cholecystitis and they are not going to be operated on with the most reasonable approach, we do not have the data, the most reasonable approach is to treat a patient conservatively, without percutaneous drainage, but to perform percutaneous drainage when the conservative treatment is failing. And the question is what are the criteria for failure. And they would be, local and general signs of inflammation are getting worse or they are not getting better over a period of time. So I mean, it is going to be very difficult to define those criteria at this meeting, but that is going to be the general direction of what we are going to do.

ENGBD

H. Neuhaus: So, concerning the technique I have two remarks.

The first remark is [regarding] the percutaneous route. I think we should aim at doing it via the transhepatic and not the transperitoneal route because of a high risk of complications due to drain dislocation. The second remark is [regarding] the endoscopic route (ENGBD), which was shown and reviewed by Dr. Tsuyuguchi today. Although I like endoscopy very much, I do not believe that the success rate of transcystic cannulation of the gallbladder is nearly 90% in the published literature. Because, before the era of laparoscopic cholecystostomy, we tried to insert naso-cystic catheters for dissolution of stones, and I know how difficult it is. I'm afraid that these data are from small series and are not based on an intention-to-treat analysis.