study process in order to improve the accuracy and completeness of reporting studies of diagnostic accuracy, and the usefulness expected.

However, to classify various kinds of categories (theraphy, prevention, aetioligy, hearm, prognosis, diagnosis, differentioal diagnosis, economic and decision analysis) and levels of evidence, it would not be much efficient with the STARD checklist. In this Guidelines, therefore, the science-based classification used in the Cocherance library (Table 2) was adopted.

Then, the evidence obtained from each item of reference was evaluated in accordance with the science-based classification used in 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. The levels 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 Bob Phillips et. al. (Table 2) [13]. The terms used in the categories are explained in Table 3.

b. Categories of Evidence and Grading of Recommendations

Based on the results obtained from these procedures, grades of recommendation were determined according to the method of classification[14-16] shown in Table ~~3~~ 4 and mentioned, as required, in the text of the Guidelines. The levels of recommendation of the reference quoted in the Guidelines are based on the Kish MA method of classification [14-16]. Recommendations graded A (that is "Do it") and B are based on a high level of evidence (that is "Probably do it"), whereas those graded D (that is "Probably don't do it") or E were considered to be not recommendable (that is "Don't do it").

ACKNOWLEGEMENT

We would like to deliver our sincere thanks to the Japanese Society for Abdominal Emergency Medicine, the Japan Biliary Association and the Japanese Society of Hepato-Biliary-Pancreatic Surgery, who provide us with great support and guidance in the preparation of the Guidelines. This process was conducted in the project on the Preparation and Diffusion of Guidelines for the Management of Acute Cholangitis (H-15-Medicine-30) with a research subsidy for fiscal 2003 and 2004 (Integrated research project for assessing medical technology) sponsored by the Japanese Ministry of Health, Labor and Welfare.

In conclusion, our deepest thanks go to the panelists who attended the International Consensus Meeting held in April 1 and 2, 2006 and gave a full cooperation in the statistification of views and comments through discussion and with answer pads as well as to the members of "Heisei no Kai".

Table1. STARD Check for the Reporting of Studies of Diagnostic Accuracy (Refered to Annals of Internal Medicine 2003, Vol. 138(1), p40-E45)

Table. STARD Checklist for the Reporting of Studies of Diagnostic Accuracy*

Section and Topic	Item #		On page #
TITLE/ABSTRACT/KEYWORDS	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 item 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.	

* MeSH = Medical Subject Heading; STARD = Standards for Reporting of Diagnostic Accuracy.

1. **Table2. Categories of Evidence (Refer to Levels of Evidence and Grades of Recommendations in the homepage of Centre for evidence-Based Medicine)**

Science-based Classification used in 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 by each literature and 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*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with > 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) 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† or validated on split-sample§§§ only	Exploratory** cohort study with good†††reference standards; CDR† after derivation, or validated only on split-sample§§§ 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*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) 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.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	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 physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Table3. Explanation of terms (Refer to Levels of Evidence and Grades of Recommendations in the homepage of Centre for evidence-Based Medicine)

Users can add a minus-sign "-" to denote the level of 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 (Randmized Controlled Trial), ARR (Absolute Risk Reduction).

* 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.

† Clinical Decision Rule. (These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category.)

‡ See note #2 for advice on how to understand, rate and use trials or other studies with wide confidence intervals.

§ 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.

§§ 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 non-exposed 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.

§§§ Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.

†† 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.

††† Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.

†††† 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 the equally or more expensive.

** 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'.

*** By poor quality prognostic cohort study we mean one in which sampling was biased in favour 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, non-objective way, or there was no correction for confounding factors.

**** Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (eg 1-6 months acute, 1 - 5 years chronic)

Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.

Table 4. 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 inconveniences (toxicity, interaction between drugs and cost).
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use

Quality of evidence	
I	Evidence from ≧1 properly randomized, controlled trial
II	Evidence from ≧ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

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Manuscript 2

The Need of the Criteria for the Diagnosis and Severity Assessment of Acute Cholangitis and Cholecystitis: Tokyo Guidelines

Running title: Standardized diagnostic criteria of acute cholangitis and cholecystitis

ABSTRACT

The Tokyo Guidelines formulates clinical guidance regarding the diagnosis, severity assessment, and treatment of acute cholangitis and acute cholecystitis for healthcare providers. It was 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 parts where data were insufficient. A working group, composed of gastroenterologists and surgeons with expertise in biliary tract surgery, supplemented with an critical care medicine, epidemiology, and laboratory medicine, were selected to formulate the draft of the 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 of the guidelines.

To build a global consensus on the management of acute biliary infection, an international expert panel that represents opinion leaders in this area was established. Between April 1 and 2, 2006, the International Consensus Meeting on acute biliary infections was held in Tokyo. The declaration of consensus was based on best available evidence, but in the part of insufficient evidence was formulated by Panel discussion.

This report describes the highlights of the Tokyo International Consensus Meeting in 2006. Some important areas highlighted at the meeting include a proposal of internationally-accepted diagnostic criteria and severity assessment for both clinical and research purposes etc.

Key words: Evidence-Based Medicine, Practice Guidelines, Acute cholecystitis, Acute cholangitis

1. Introduction

More than 100 years have elapsed since Charcot's triad (1877) [1] was first proposed as characteristic findings of acute cholangitis and the Murphy's sign (1903) [2] as a diagnostic method of acute cholecystitis. Despite tremendous contribution from basic research on acute biliary infection, and improvement in diagnostic techniques and treatment, acute cholangitis may still be fatal. One of the reasons might be wide variations in the clinical practices of acute biliary infection in every part of the world. [3-10] If there were "the best treatment", such variation may imply low quality of medical care.

Evidence-based medicine (EBM), which is the application of current best evidence from clinical research to the management of patient care, is looked upon as a new paradigm, replacing the traditional medical paradigm which is based on authority. The most realistic and efficient use of EBM by clinicians at the point of care involves accessing and applying valid and relevant summaries of research evidence, i.e. evidence-based practice guidelines. In order to avoid unfavorable practice pattern by integrating clinical experience with the best available research information, the Research Group for Health and Labor Sciences Research in Japan (Research on the Preparation and Diffusion of Guidelines for the Management of Acute Biliary Infection, (principal investigator: Tadahiro Takada) set up a working group in July 2003, with support of the Japanese Society for Abdominal Emergency Medicine and the Japan Biliary Association and the Japanese Society of Hepato-Biliary-Pancreatic Surgery. The working group consisting of not only the specialists of gastroenterology and surgery, but also those of intensive care, pediatrics, laboratory medicine, clinical epidemiology and healthcare economics had been organized to formulate the "Evidence-based Clinical

Practice Guidelines for the Management of Acute Biliary Infection".

From the literature review, we have found scarce evidence on the management of acute biliary infections and treatment strategies. Therefore we needed to hold an international consensus meeting, Tokyo 2006, to complement the insufficient area of the high-level evidence.

This article describes the necessity of Tokyo guidelines for the management for cholecystitis and cholangitis that were concreted through the International Consensus Meeting held in Tokyo April 1-2, 2006.

2. The necessity for standardized diagnostic criteria

In the Guidelines, we proposed internationally accepted the diagnostic criteria of acute cholangitis and cholecystitis. Although the Charcot's triad (abdominal pain, fever and jaundice)" has been historically used as the diagnostic criteria of acute cholangitis, it has been pointed out that no more than 70% of acute cholangitis patients show the triad. Reynold's pentad, which was proposed by Reynold et al. in 1959 as a definition of acute obstructive cholangitis, is noted only in several percent of the cases.

Regarding the well-known diagnostic finding of Murphy's sign in cholecystitis, the sensitivity and specificity of Murphy's sign were 65% and 87%. Therefore it is difficult to diagnose acute cholecystitis based only on clinical signs such as Murphy's sign.

These facts show the lack of the universal definition, then we realized the necessity of more practical diagnostic criteria.

3. The necessity for severity assessment

Severe acute cholangitis was often defined with Reynolds' pentad which is composed of

Charcot's triad plus shock and disturbance of consciousness 2. But the incidence of pentad is extremely rare in patients with acute cholangitis that is reported less than 10% even in severe cases (Table 2) ref. Previously, the term, acute obstructive suppurative cholangitis (AOSC), was used for cholangitis which presents all components of Reynolds' pentad and is the most severe form of the disease. Longmire et al17 classified acute suppurative cholangitis into two categories, one is the cases who present Charcot's triad, the other is the cases who presented mental confusions and shock together with the triad. The latter represents severe acute cholangitis but the definition is vague and confusing ref.

The mortality rate of acute cholangitis was reported with a wide spectrum, ranging from 2.5% to 65% in literatures, probably due to the lack of standard definition of severity (Table 5) [Ref]. Thus severity assessment criteria is necessary for early identification of patients with potentially life-threatening illness and appropriate management which includes transfer to the referral hospital and emergent biliary drainage.

Murphy's sign has been often used in the diagnosis of acute cholecystitis. However, Murphy sign is only useful when other physical findings are equivocal as in mild cholecystitis. On the othre hand, right upper quadrant tenderness, muscle guarding, and rebound tenderness are the signs more frequently seen in acute cholecystitis according to the extent of peritoneal irritation which would be severe cholecystitis. Therefore severity assessment for acute cholecystitis is necessary for performance of early intervention.

Organ failure scores, such as Marshall's MOF score, SOFA score, are sometimes used to evaluate organ failures in critically ill patients. But in this severity assessment of acute cholangitis, using these score is cumbersome, and moreover there is not enough evidence that each cut off point is meaning value in assessment of severity of the disease. Moreover in both scores serum bilirubin is used as an index of liver failure, however hyperbilirubinemia may be always present in acute cholangitis causing overestimation of these system. On the other hand, severity of acute cholecystitis is milder than that of acute cholangitis, in severity score of cholecystitis, image changes associated with acute cholecystitis are used rather than systemic symptoms, nor organ failure score. Therefore, at this point, we formulated a simple severity assessment

criteria in considering MODS scores. In future, severity scores based on these organ failure scores may show significant value in evaluation of the patients in severity of acute cholangitis.

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Manuscript 3

Definition, Pathophysiology and Epidemiology of Acute Cholangitis and Cholecystitis: Tokyo Guideline

Running title: Definition, Pathophysiology and Epidemiology in Tokyo guideline.

Abstract

This paper discusses the definition, pathophysiology and epidemiology of acute cholangitis and cholecystitis. Acute cholangitis and cholecystitis originate mostly in bile dust stone and gallstone, whereas acute cholecystitis is attributable to many other causes, including micro-circulatory insufficiency, chemical disorders associated with drugs, infections by microorganism, protozoon and parasites, collagen disease and allergic reaction. Particularly for acute acalculous cholecystitis, surgery, trauma, burn and parenteral nutrition are risk factors. The factors associated with the onset of cholelithiasis include obesity, age and drugs such as oral contraception.

The reported mortality of less than 10% of acute cholecystitis cases gives an impression that it is not a fatal disease except elderly and/or acalculous cases. However, there are some references reporting high mortality of cholangitis, although the mortality differs greatly depending on the year of report and the severity of the disease. Even the reports published in and after the 1980's indicate the high mortality ranging from 10 to 30% of the cases with multi-organ failure due to irreversible shock as a major cause of death.

As many of the reports on acute cholecystitis and cholangitis use different standards, it is difficult to compare. Especially, great variations in treatment results and mortality indicate the necessity of standardized diagnostic and severity assessment criteria.

Key words; Definition, pathophysiology, epidemiology, cholangitis, cholecystitis

Introduction

Acute biliary infection is a systemic infectious disease which sometime becomes fatal and requires prompt treatment. The first report on acute biliary infection was Charcot's "The symptom of hepatic fever" (1877). Over the last 10 decades, Charcot's triad has been used broadly in clinical setting, and the diagnosis and treatment techniques and intensive treatment methods have been improved remarkably, but mortality still remains as high as at the level of 10 – 30%.

In the process of establishing the Guidelines, it became evident that there were neither globally accepted guidelines for the management of acute cholangitis and cholecystitis nor the criteria of severity assessment. It was anticipated that the production of them may be able to reduce the mortality of these diseases.

This paper proposes the guidelines with the evidences collected with a focus on the definition, pathophysiology and epidemiology of acute cholangitis with repeated discussions in the working group. When there is insufficient evidence to properly reply to the clinical questions, it was supplemented by the feedback from the consensus discussion in the working group and the open symposium.

1. Definition and Pathophysiology

1. Acute cholangitis

Definition

Acute cholangitis is a morbid condition with acute inflammation in the bile duct. The onset of acute cholangitis involves two factors (i) remarkably increased bacteria in the bile duct, (ii) elevated intraductal pressure of the bile duct to allow backward flow of bacteria or endotoxin into the blood vessel (cholangio-venous reflux).

Pathology of cholangitis

Because of its anatomical characteristics, the biliary system is likely to be affected by the elevated intraductal pressure of the bile duct. In acute cholangitis, the bile ductule tends to rapture under elevated intraductal pressure of the bile duct and induce the flow of bile contents into the sinusoid and then into blood. Advanced inflammation often progresses to serious and fatal infection such as hepatic abscess and sepsis.

The cases, who show from early stage the signs of multiple organ failure (renal failure, DIC, disturbance of consciousness and shock) as well as the symptoms generally known as acute cholangitis symptoms (fever accompanied by chills and

shivering, jaundice and abdominal pain), who do not respond to conservative treatment, and who present factors implying aggravation, should undergo "emergent biliary drainage on early stage" for lifesaving [1]. We have to keep in mind that unless early and appropriate biliary drainage is performed, systemic conditions in severe cholangitis cases may be getting worse rapidly to result in a tragic outcome.

A. Changes in the description of acute cholangitis

(1) The symptom of hepatic fever: the term used for the first time by Charcot[2] in his report published in 1887. Intermittent fever accompanied by chills, right upper quadrant pain and jaundice were termed later as Charcot's triad.

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

(3) Classification by Longmire [4]: Longmire classified the cases with only three symptoms, intermittent fever accompanied by chills and shivering, right upper quadrant pain and jaundice as acute suppurative cholangitis, and the cases, who present lethargy or mental confusions and shock as well as the triad as acute obstructive suppurative cholangitis (AOSC). He also reported that the latter corresponded to the morbidity of acute obstructive cholangitis as defined by Reynolds[4], and classifies acute microbial cholangitis as follows:

I. Acute cholangitis extended from acute cholecystitis
II. Acute non-suppurative cholangitis
III. Acute suppurative cholangitis
IV. Acute obstructive suppurative cholangitis
V. Acute suppurative cholangitis accompanied by hepatic abscess

B. Other morbidity to be carefully monitored: Special cholangitis

(1) Cholangitis by Mirizzi Syndrome

This 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 [5].

Type I: A morbid condition with the bile duct pressed from the left by the presence of stones in the gallbladder neck and cystic ducts and pericholecystic inflammatory change

Type II: A morbid condition with biliobilary fistulation caused by pressure necrosis of the bile duct due to cholecystolithiasis

(2) Lemmel Syndrome

A series of morbid conditions in which duodenal parapapillary diverticulum presses or displaces the bile duct or pancreatic duct (its opening) and obstruct the passage in the bile or hepatic duct, thereby causing cholestasis, jaundice, gallstone, cholangitis and pancreatitis [6].

2. Acute cholecystitis

Definition:

Acute inflammatory disease of the gallbladder. It is often attributable to gallstones, but many factors, such as disturbed blood circulation in the gallbladder, chemical injury, infections by microorganism, protozoon and parasites, collagen disease and allergic reaction are involved.

A. Classification of acute cholecystitis by pathology and morbidity

(1) Edematous cholecystitis: 1st stage (2-4 days)

Cholecystitis having epistatis and the dilated capillary tubes and lymphatic vessels as main morbidities and characterized by the epistatic and edematous gallbladder wall. Gallbladder tissue is intact histologically, but dilated micro vessels and remarkable edema in the subserous layer are observed.

(2) Necrotizing cholecystitis: 2nd stage (3-5 days)

Cholecystitis with edematous changes followed by the necrotizing hemorrhage of tissue. When the gallbladder wall is pressed by the elevated internal pressure, the blood flow of the artery branches is obstructed (histologically, thrombus formation in the microvessel followed by closure) to necrotize the tissue. Histologically, dotted necrosis is observed here and there in the layer, but necrosis of the entire or broader area in the layer is scarcely observed.

(3) Suppurative cholecystitis: 3rd stage (7-10 days)

Cholecystitis in which white blood cells permeate in the necrotic tissue and suppuration begins. On this stage, with active repairing of inflammation being under way, the enlarged gallbladder begins to contract, and the wall is thickened again due to fibrous growth accompanying inflammation. Intra-wall abscess is relatively large, and that with abscess deep in the gallbladder wall is pericholecystic abscess.

(4) Chronic cholecystitis

Chronic cholecystitis occurs after repeated occurrence of mild attack of cholecystitis,