

## INTRODUCTION

Acute cholangitis presents in a wide spectrum of severity, ranging from relatively mild cases to severe cases accompanied by hypotension and disturbed consciousness. It is reported that when no appropriate biliary drainage was available in 20 – 30 years ago, the mortality of conservative treatment for acute cholangitis was extremely high (Table 1). There is no RCT (randomized controlled trial) comparing conservative treatment and biliary drainage. However, it is evident that many of patients with acute cholangitis cannot be saved by the 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 paper reviews the past references regarding biliary drainage methods and discusses the methods and timing of biliary drainage for acute cholangitis, with a principle of evidence based medicine.

**Table 1. Mortality of acute cholangitis patients subjected to conservative treatment**

Author	Mortality rate by conservative therapy
O'Connor MJ <sup>1)</sup>	87%
Welch JP <sup>2)</sup>	100%

### **Q1. How do we select the mode of biliary drainage? Endoscopic vs percutaneous vs open?**

Endoscopic biliary drainage: Recommendation grade A

Percutaneous transhepatic biliary drainages: Recommendation grade B

Biliary drainage includes three different kinds of procedure: endoscopic, percutaneous transhepatic, and open drainage. The safety and usefulness of endoscopic drainage have been proved by many studies (level 2b)<sup>3</sup>(level 4)<sup>4-6)</sup>. One RCT<sup>3)</sup> was conducted to compare endoscopic and open drainages in 82 severe acute cholangitis patients with hypotension and disturbed consciousness. This RCT demonstrated that 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 is safer and more effective than open drainage (Table 2) (level 2b). Although there are no recent reports on open drainage, “Current Surgical Therapy, 8th edition”<sup>7)</sup> describes that the endoscopic or interventional radiological (IVR) drainage is superior to open drainage.

Chen et al<sup>8)</sup> performed percutaneous transhepatic biliary drainage (PTBD) on 56 acute cholangitis patients, and observed noticeably improved clinical conditions in 46 patients (82.1%), with disappearance of fever within 18 – 24 hours (level 4). Pessa et al<sup>9)</sup> also performed PTBD in 42 acute cholangitis patients, and reported the success rate of 100%, morbidity of 7%, and mortality of 5% (level 4). Though the usefulness of percutaneous transhepatic drainage is recognized widely, all of the previous

reports were retrospective case series studies (level 4) <sup>8-16)</sup>.

As there is no RCT comparing endoscopic and percutaneous drainage, definitive conclusion on better procedure has not been reached. However, considering few occurrence of serious complications such as intraperitoneal hemorrhage and biliary peritonitis<sup>4-6)</sup>, and shorter duration of hospitalization<sup>17)</sup>, endoscopic drainage is preferred whenever it is available and applicable (level 4) <sup>17, 18)</sup> (level 3a) <sup>19-21)</sup>. Anyway, as both procedures require experienced hand, a drainage method selected should be contingent upon the availability of this resources and manpower so that it could be delivered successfully with good outcome at each institution.

**Table 2. Drainages for acute cholangitis – Endoscopic vs. open drainage<sup>3)</sup>**

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

**Q2. What procedure of endoscopic biliary drainage should be used? External (nasobiliary drainage) or internal drainage? EST vs no EST?**

Either ENBD or biliary tube stent placement can be used.

Addition of EST should be determined according to the patient conditions and operators skills.

One RCT (level 2b) <sup>22)</sup> comparing ENBD and biliary tube stent placement (EST was not added in both cases) showed no significant difference in success rate, effectiveness, and morbidity, but revealed that the incidence of tube troubles such as removal of the tube by patients themselves tended to be higher in ENBD, and patient’s discomfort was significantly lower in the stent placement. From these findings, for patients who are likely to remove the ENBD tube by themselves the stent placement is preferable <sup>22)</sup>.

Endoscopic biliary drainage methods applicable for choledocholithiasis-induced acute cholangitis, most frequently encountered disease in 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) <sup>23, 24)</sup> 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 patient’s condition and the number and diameter of stones into account.

**Table 3 Endoscopic biliary drainage -With EST group vs. without EST group-**

Author (year) (Procedure)	No. of cases	No EST added			EST added			
		Success rate (%)	Effectiveness (%)	Incidence of complications ** (%)	No. of cases	Success rate (%)	Effectiveness (%)	Incidence of complications ** (%)
Sugiyama (1998) <sup>23)</sup> (ENBD, 7Fr)	93	96	94	2	73	95	92	11
Hui (2003) <sup>24)</sup> (Stent, 7Fr)	37	86	100	3	37	89	100	11

\* Complications associated with technique, such as bleeding and pancreatitis

### Q3. What is the indication of open drainage?

Open drainage should only be used in patients for whom endoscopic or percutaneous transhepatic drainage is contra-indicated or was unsuccessfully performed. In such difficult condition, the primary goal is to decompress the biliary tract expeditiously. It is important to emphasize shortening operative time and minimizing surgical invasiveness. For this sake, it is recommended to complete operation quickly by placing a T-tube without spending long time for lithotomy<sup>25)</sup> (level 4).

### Q4. Is prophylactic cholecystectomy necessary after choledocholithiasis is successfully treated in acute cholangitis?

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

Boerma et al conducted a RCT (level 2b)<sup>26)</sup> to assess clinical value of prophylactic laparoscopic cholecystectomy in patients whose choledocholithiasis was successfully treated with EST (all patients had gallbladder stone). Symptoms related to cholecystitis appeared in 27 of 59 patients (47%) who had not undergone prophylactic laparoscopic cholecystectomy, and eventually 22 of the 27 underwent cholecystectomy. Thus, they concluded that prophylactic cholecystectomy is of clinical value.

It has been reported that the incidence of cholecystitis in patients whose gallbladder with stone was left after EST was 7.6-22% (level 2b)<sup>27-30)</sup> (Table 4). This value 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 subsequent recrudescence of severe acute cholangitis or acute cholecystitis with attending high fatality. In case of acalculous gallbladder, the incidence of cholecystitis is low, around 1%, so that no cholecystectomy is required (level 2b)<sup>27-30)</sup> (Table 4).

**Table 4 Incidence of acute cholangitis after endoscopic treatment of choledocholith**

Calculus gallbladder	Acalculus gallbladder	Average observation period (year)
5.8%(11/190)	— —	6.8 年 <sup>27)</sup> *
7.6%(34/448)	1.2%(3/246)	7.5 <sup>28)</sup>
12%(2/17)	0%(0/15)	14.5 <sup>29)</sup>
22% (7/32)	1%(1/88)	10.2 <sup>30)</sup>

\*: Whether all population is calculous gallbladder or not is unknown.

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**Diagnostic Criteria and Severity Assessment of Acute Cholecystitis:  
Tokyo Guidelines**

**Running title: Diagnosis and severity assessment of acute cholecystitis**

## **Abstract**

The aim of this article is to propose new diagnostic criteria and severity assessment of acute cholecystitis as a result of systematic review of literatures and expert consensus opinions. A working group reviewed articles with regard to the diagnosis and treatment of acute cholecystitis and extracted the best current available evidence in this area. In addition to the evidence and face-to-face discussions, domestic consensus meetings were held by the experts in order to assess the outcome. Final outcome statement regarding the diagnostic criteria and severity assessment was clarified through the International Consensus Meeting in Tokyo 2006.

The case showing two of the clinical manifestations such as (1) (Murphy's sign, fever, right upper quadrant: mass/pain/tenderness, rigidity/muscle guarding, rebound tenderness) and one of the laboratory data such as (2) (elevated or decreased white blood cell count, or elevated C-reactive protein) is diagnosed as suspected acute cholecystitis. The case whose findings are confirmed by imaging study is diagnosed as acute cholecystitis.

The severity of acute cholecystitis is classified into 3 types and are defined as: those, who are associated with organ dysfunction, requiring early/urgent intervention (operation and/or drainage) and organ support are defined as "severe", those, who are associated with moderate local complication (pericholecystic fluid collection, irregular gallbladder wall, serious thickening of the gallbladder wall), requiring early/urgent intervention (operation and/or drainage) as "moderate", and those who can be observed under conservative medical treatment as "mild".

**Key Words:** Acute cholecystitis, Diagnostic criteria, Severity assessment

## I. Introduction

Expedient diagnosis allows early commencement of treatment and reduces both mortality and morbidity. The accurate diagnosis of not only typical but also atypical cases requires the diagnostic criteria. Also, acute cholecystitis has relatively better prognosis than acute cholangitis, but may require immediate management, in severe cases of torsion of the gallbladder, and emphysematous, gangrenous and suppurative cholecystitis. The lack of standard criteria of diagnosis and severity assessment is reflected by the wide range of reported mortality rate in literatures, and makes it impossible to provide homogeneous best treatment for the patients with this disease. In this manuscript we propose new diagnostic criteria and severity assessment of acute cholecystitis based on the best available evidence and expert's consensus which is achieved through the International Consensus Meeting for the Management of Acute Cholecystitis, Cholangitis held in April 1-2, 2006 in Tokyo.

## II. Diagnostic criteria for acute cholecystitis

Diagnosis is a starting point in the management of acute cholecystitis, and prompt and timely diagnosis may lead to early commencement of treatment, and lower mortality and morbidity. For accurately diagnosing not only typical but also atypical cases, the diagnostic criteria are necessary. The Guidelines establish the diagnostic criteria for acute cholecystitis as follows (Table 1).

**Table 1. Diagnostic criteria of acute cholecystitis**

- |   |
|---|
| <p>① : 1) Murphy' s sign, 2) fever, 3) right upper abdominal quadrant : mass/pain/tenderness, 4) rigidity/muscle guarding, 5) rebound tenderness</p> <p>② : 1) elevated or decreased WBC count, 2) elevated CRP</p> <p>③ : Imaging findings characteristic to acute cholecystitis</p> |
|---|

Suspected diagnosis : Two items in ① and one item in ② are positive.

Definite diagnosis : ③ is confirmed in patients with the above suspected diagnosis.

Note: Acute hepatitis, other acute abdomen and chronic cholecystitis should be excluded.

### \*Imaging findings of acute cholecystitis

**Ultrasonic examination:** Sonographic Murphy sign (pain cause by pressing the gallbladder by ultrasonographic probing), thickened gallbladder wall (>4 mm) (if the patient has not chronic liver disease and/or ascites), enlarged gallbladder (long axis diameter>8 cm, short axis diameter>4 cm) , incarcerated gallstone, debris echo, pericholecystic fluid collection, sonolucent layer at the gallbladder wall, striated intramural lucencies, and Doppler signals<sup>1-4)</sup>.

**CT :** Thickened gallbladder wall, pericholecystic fluid collection, enlarged gallbladder, linear



high-density areas in the pericholecystic fat tissue<sup>5)</sup>.

**MRI:** Gallstone, pericholecystic high signal, enlarged gallbladder, thickened gallbladder wall<sup>6-8)</sup>.

### **III. Severity assessment of acute cholecystitis and transfer criteria of the patients**

#### **A. Concept of severity grading of acute cholecystitis**

Acute cholecystitis may present as anything from a mild and self-limited illness to a fulminant and potentially life-threatening illness. The latter requires an appropriate management including intensive care and urgent treatment (operation and/or drainage) for saving life. Thus, severity assessment is clearly important for clinical management of acute cholecystitis. In this paper we classified severity grade into the following 3 categories; “severe”, “moderate” and “mild”.

##### **(1) Severe acute cholecystitis**

Cholecystitis, which is associated with organ dysfunction or severe complications, requiring early/urgent intervention (operation and/or drainage) and organ support.

##### **(2) Moderate acute cholecystitis**

Cholecystitis, which is associated with moderate local complication, requiring early/urgent intervention (operation and/or drainage).

##### **(3) Mild acute cholangitis**

Cholecystitis, which can undergo conservative medical treatment.

#### **B. Prognosis predictors**

It is difficult to define prognosis predictors, because there are only a few fatal cases. In this paper, “factors observed at a significantly higher frequency in gangrenous cholecystitis” and “factors observed at a significantly higher frequency in cases with severe cholangitis, biliary peritonitis, or biliary infection” are defined as “prognosis predictors” (Table 2) .

**Table 2. List of prognosis predictors in acute cholecystitis**

Factor	Criteria	Reference	Level	
• Organ failure	blood urea nitrogen	>40 mg/dL	9)	4
	bilirubin	>5 mg/dL	10)	4
• Inflammatory reaction, infection	white blood cell count	>14,100 /mm <sup>3</sup>	10,11)	4
		>15,000 /mm <sup>3</sup>	12)	4
	body temperature	>37.3°C	10)	4
	C-reactive protein	>10 mg/dL	13)	1b
• Diagnostic imaging				
1) severe inflammatory changes in the gallbladder wall				
pericholecystic fluid collection		15-17)		3b-4
radial pericholecystic high signal (MRI)		18)		4
irregular gallbladder wall (CT)		17)		3b
poor contrast of the gallbladder wall (CT)		17)		3b
severe thickening of the gallbladder wall	>7.8 mm	17)		3b
2) serious local complications				
pericholecystic abscess		15)		4
hepatic abscess		15)		4
dilated bile duct		15)		4
3) others				
severe gallbladder enlargement	short-axis dimension>5 cm	17)		3b
• Others				
age	>50, >65	11,13)		1b-4
diabetes		11,12)		4
male		11)		4
history of cardiovascular disease		11)		4
low serum iron level	<38 µg/dL	14)		4
high alanine aminotransferase level	>50 U/L	12)		4
high alkaline phosphatase level	>200 U/L	12)		4

### C. Criteria for the severity assessment

Acute cholecystitis has relatively better prognosis as compared with acute cholangitis, but may require prompt treatment for gangrenous cholecystitis, emphysematous cholecystitis and torsion of the gallbladder. The progression of acute cholecystitis into severe form means the occurrence of multiple organ dysfunction syndrome (MODS). Organ dysfunction scores, such as Marshall's MOF score, SOFA score, are sometimes used to evaluate organ dysfunction in critically ill patients. In the Guidelines, severity is classified into three grades: those requiring early/urgent intervention (operation and/or drainage) and organ support are defined as "severe", those requiring early/urgent intervention (operation and/or drainage) are defined as "moderate", and those who can be observed under conservative medical treatment as "mild" (Table 3). When the patient is accompanied by acute cholangitis, the criteria for the severity assessment of acute cholangitis should also be taken into account. "Elderly" is not a factor indicating the severity itself, but it indicates a propensity to progress to a severe form. It is not included therefore in the severity assessment criteria.

**Table 3. Severity assessment criteria for acute cholecystitis**

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**Severe acute cholecystitis**

“Severe” acute cholecystitis is accompanied by at least one of the following organ dysfunctions or severe complications.

**I. Organ Dysfunctions**

- ① Cardiovascular dysfunction (Hypotension)
- ② Neurological dysfunction (Disturbance of consciousness)
- ③ Respiration dysfunction ( $\text{PaO}_2/\text{FiO}_2$  ratio  $< 300$ )
- ④ Renal dysfunction (Oliguria, Creatinine  $>2.0$  mg/dL)
- ⑤ Hepatic dysfunction (Bilirubin  $> 5.0$  mg/dL)
- ⑥ DIC (Platelet  $< 100,000/\text{mm}^3$ )

**II. Local Complications**

- ① Biliary peritonitis
- ② Pericholecystic abscess
- ③ Hepatic abscess

**III. Severe Inflammatory Changes of the Gallbladder Wall**

- ① Gangrenous cholecystitis
  - ② Emphysematous cholecystitis
  - ③ Suppurative cholecystitis
  - ④ Torsion of the gallbladder
  - ⑤ Perforation of the gallbladder
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**Moderate acute cholecystitis**

“Moderate” acute cholecystitis is accompanied by at least one of the following conditions.

- ① Pericholecystic fluid collection
  - ② Irregular gallbladder wall
  - ③ Serious thickening of the gallbladder wall
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**Mild acute cholecystitis**

“Mild” acute cholecystitis does not meet the criteria of “severe” and “moderate” acute cholecystitis.

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Note: Jaundice, whose severity rises by cholecystitis itself is likely to progress to serious particularly at the bilirubin  $>5$  mg/dL (bile infection rate is high).

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**Antimicrobial therapy for Acute cholecystitis : Tokyo Guideline for  
Management of Acute Cholangitis and Cholecystitis**

**Running title : Antimicrobial therapy for cholecystitis**

## **Abstract**

Acute cholecystitis consists of various morbid conditions, ranging from mild cases that are relieved by oral administration of antimicrobial drugs or even without antimicrobials to severe cases complicated by biliary peritonitis. Microbial cultures should be performed by collecting bile at all available opportunities to identify the species of both aerobic and anaerobic bacteria. Empirically selected antimicrobials should be administered. Antimicrobial activity against potential causative organism, severity of cholecystitis, the past history of antimicrobial administration of the patient, and the past history of causative organism detection in the relevant institution must be taken into consideration for choice of antimicrobial drugs. In mild cases which are closely mimic to biliary colic, the administration of NSAIDs is recommended for preventing the progression of inflammation (Recommendation grade A). When a causative organism is identified, the drug should be changed to a narrower-spectrum antimicrobial drug depending on the species and its sensitivity.

**Key Words:** Acute cholecystitis, Primary care, Antimicrobial therapy, Guidelines

## **Clinical Questions**

- Q1. What microbiologic studies should be performed in acute cholecystitis?
- Q2. How to use antimicrobial agents for patients with acute cholecystitis?
- Q3. Is administration of NSAIDs to patients suffering an attack of biliary colic effective at preventing the development of acute cholecystitis?
- Q4. What are the important factors for consideration in antimicrobial drug selection?
- Q5. Should penetration into the bile or gallbladder wall be considered in the selection of therapeutic antimicrobials in acute cholecystitis?
- Q6. What is the result of clinical trials regarding antimicrobial therapy?
- Q7. What are the current recommendations for antimicrobial therapy in acute cholecystitis?

## **Introduction**

Acute cholecystitis consists of various morbid conditions, ranging from mild cases that are relieved by oral administration of antimicrobial drugs or even without antimicrobials to severe cases complicated by biliary peritonitis, each of which requires a different treatment policy. Decisions regarding antimicrobial therapy must be made based upon a knowledge of the likely infecting microorganisms, the pharmacokinetics and toxicities of available agents, and results of local antimicrobial susceptibility testing. The severity of illness and history of exposure to antimicrobials are also key factors in determining appropriate therapy. Needless to say, whatever antimicrobial drug is prescribed, great care should be given to the microbial substitution and the emergence of drug-resistant bacteria, and therefore long-term administration without acceptable rationale should be avoided.

In this paper we discuss a basic treatment policy for acute cholecystitis, together with primary care and antimicrobial therapy. Although a lack of randomized controlled trials (RCTs) of antimicrobials is another important problem, we propose consensus- and *in vitro* activities-based guidelines for empirical antimicrobial selection for acute cholecystitis.



**Q1. What microbiologic studies should be performed in acute cholecystitis?**

- Bile and blood culture should be performed at all available opportunities.

Clinical significance of microbial examination in acute cholecystitis depends on the severity of disease. Although most of the mild and moderate cases are curable without microbial information, biliary infection is associated with post-operative complications and mortality rates in severe cases or biliary stones (level 2b-3b). Positive bile culture is correlated with the progression of cholecystitis to a severe form (level 2b-3b) <sup>1,2</sup>. Therefore, especially in severe cases, gallbladder bile should be collected at the time of operative, laparoscopic, or percutaneous intervention for culture and susceptibility testing. A sample of gallbladder wall should be separately sent for culture. Aerobic cultures only should be obtained. Bacterial culture positive rate in acute cholecystitis are demonstrated in Table 1, Chapter 5 (p000).

The importance of blood culture results is relatively limited in acute cholecystitis, since the microorganisms found in this infection are not highly invasive pathogens (as, for example, *Staphylococcus aureus*) and therefore the presence of positive blood cultures do not alter the agents used or the duration of treatment. Furthermore, the microorganisms identified in the blood do not exclude other microorganisms being present in the gallbladder infection and therefore do not limit the agents administered.

**Q2. How to use antimicrobial agents for patients with acute cholecystitis?**

- Antimicrobial agents should be administered to all cases diagnosed as acute cholecystitis.
- Antimicrobial agents should be administered as soon as the diagnosis of acute cholecystitis is established.
- Full-dose antimicrobial agents should be administered intravenously.

Mild cases, with little abdominal pain and inflammatory findings and closely mimic to biliary colic, may be observed with oral antimicrobial drugs or even without antimicrobials. In this case, the administration of NSAIDs is recommended, as described below.

**Q3. Is administration of NSAIDs to patients suffering an attack of biliary colic effective at preventing the development of acute cholecystitis?**

Administration of NSAIDs to cases with the attack of biliary colic is recommended to prevent the onset of acute cholecystitis (Recommendation grade A).

NSAIDs, such as diclofenac or indomethacin, should be used in the primary care due to its analgesic effect and inhibition of prostaglandin release from gallbladder wall. An RCT of NSAIDs administration (75 mg of diclofenac, intramuscular injection) for the cases with biliary colic attack showed that they have the effect to relieve pain and prevent the progression to an acute form (level 1b) <sup>3</sup>. Although it has been reported that NSAIDs effectively improve gallbladder functions in chronic cholangitis cases (level 3a) <sup>4</sup>, there is no report to date on NSAIDs administration after the onset of acute cholecystitis improves the disease.

**Q4. What are the 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 of the patient
  - (5) Past detection of causative bacteria in the institution
- When a causative organism is identified in microbial culture tests, the drug should be changed to a narrower-spectrum antimicrobial drug targeted the species and its sensitivity.

The dose of antimicrobial agents should be reduced for cases with reduced renal functions. Since most of cephem, penicillin, aminoglycoside and carbapenem antimicrobial drugs are excreted by kidneys, the dose is reduced for patients with nephropathy. “The Sanford Guide to antimicrobial therapy 2005” <sup>5</sup> recommends the following dosages:

**Estimate dose for adult males (×0.85 for females)**

= % of the dose for those with normal kidney function

=  $(140 - \text{age})(\text{optimum body weight (kg)}) / (72)(\text{serum creatinine mg/dl})$

Male optimum body weight:  $50.0\text{kg} + 0.91\text{kg/cm}(150\text{cm and taller})$

Female optimum body weight:  $45.5\text{kg} + 0.91\text{kg/cm}(150\text{cm and taller})$

Drug dosage adjustment is not necessary for ceftriaxone and ciprofloxacin in patients with renal failure. By contrast, a dose adjustment of ceftriaxone may be indicated in patients with hepatic impairment <sup>5</sup>.

**Q5. Should penetration into the bile or gallbladder wall be considered in the selection of therapeutic antimicrobials in acute cholecystitis?**

There is a common belief that antimicrobial agents with excellent penetration to gallbladder wall should be chosen for antimicrobial therapy. In Table 3, we showed antimicrobial agents with good penetration.

**Table 1** Intravenous antimicrobial drug with good penetration into the gallbladder wall (level 4) <sup>5</sup>

<b>Penicillins</b>	Ampicillin, Piperacillin, Piperacillin/tazobactam
<b>Cephems</b>	
(1st generation)	Cefazoline
(2nd generation)	Cefmetazole, Flomoxef, Cefotiam,
(3rd,4th generation)	Cefoperazone/Sulbactam <sup>6</sup> , Ceftriaxone <sup>7</sup> , Ceftazidime, Cefpirome, Cefozopran
<b>New quinolones</b>	Ciprofloxacin <sup>6</sup> , Pazufloxacin
<b>Monobactams</b>	Azthreonam <sup>8</sup>
<b>Carbapenems</b>	Meropenem, Panipenem/betamipron
<b>Lincosamides</b>	Clindamycin <sup>9</sup>

However, there are no clinical or experimental data to support this. Especially, in cases with acute cholecystitis, the inflammation of gallbladder wall leads to permeability changes in terminal capillaries and post-capillary venules, resulting in diffusion of the agents from blood into the extravascular area of infection. Thus the high concentration of the antimicrobials in the gallbladder wall and bile may be achieved, even if its biliary penetration is supposed to be poor.

#### **Q6. What is the result of clinical trials regarding antimicrobial therapy?**

There are three RCTs which evaluate the effect of antimicrobial agents for patients with acute cholecystitis (Table 2) (level 2b) <sup>10-12</sup>, and all of them demonstrated that recently developed antimicrobial drugs had equivalent effectiveness and usefulness as ampicillin and aminoglycoside, which was regarded as a standard regimen for cholecystitis in the 1980s (level 4-5) <sup>13,14</sup>. Therefore, according to the clinical trials available so far, ampicillin and aminoglycoside, piperacillin, and several cepheims are recommended for treatment of acute cholecystitis (Recommendation grade A).

**Table 2. Clinical comparative test between antimicrobial drugs in cholecystitis**

Authors (Year)	Subjects	Antimicrobial	Clinical cure rate	Significant difference
Muller(1987) <sup>10</sup>	Cholecystitis	ABPC+TOB	11/13 (85%)	
		piperacillin	18/19 (95%)	ns

Chacon(1990) <sup>11</sup>	Cholecystitis + cholangitis	cefoperazone	19/20 (95%)	ns
		Pefloxacin	49/50 (98%)	ns
		ABPC+GM	45/47 (95.7%)	
Thompson(1993) <sup>12</sup>	Cholecystitis + cholangitis	cefepime	78/80 (97.5%)	ns
		Mezlocillin+GM	40/40 (100%)	

ABPC: ampicillin, TOB: tobramycin, GM: gentamicin

However, there is only one RCT which solely focused acute cholecystitis. In addition, widely used antimicrobial agents at present for acute cholecystitis, including penicillin/ $\beta$ -lactamase inhibitors, carbapenems and the 3rd and 4th cepheems, are not tested in these RCTs. In this regard, we recommend the alternative regimens of antimicrobial agents in the Tokyo Guidelines in a consensus-based manner, as follows.

#### Q7. What are the current recommendations for antimicrobial therapy in acute cholecystitis?

- Antimicrobial drugs should be selected according to the severity assessment.
- Empirically administered antimicrobial drugs should be changed to more appropriate agents, according to the identified causative microorganisms and their sensitivity to antimicrobials.

##### 1) Mild cases (refer to Manuscript 8)<sup>15</sup>

Mild cases are often caused by a single intestinal organism such as E coli, and therefore monotherapy of one of the following antimicrobial drugs is recommended. Since intestinal organisms resistant to penicillins and cefazoline are likely to be produced, use of penicillin/ $\beta$ -lactamase inhibitor, such as piperacillin/tazobactam<sup>16</sup>, or ampicillin/sulbactam is recommended.

##### <Example of Uses >

Oral new-quinolones	Levofloxacin, Ciprofloxacin
Oral cepheems	Cefotiam, Cefcapene
First-generation cepheems	Cefazoline
Wide spectrum penicillin/ $\beta$ -lactamase inhibitor	Piperacillin/tazobactam, Ampicillin/sulbactam

Mild acute cholecystitis cases, with a relatively mild abdominal pain and little inflammatory findings on laboratory data and imaging, and closely mimic to biliary colic, may be observed with oral antimicrobial drugs or even without antimicrobials.