# Tokyo Guidelines and Their Limits

5

Kohei Mishima and Go Wakabayashi

## 5.1 Diagnostic Criteria and Severity Grading of Acute Cholecystitis

The diagnostic criteria and severity grading of acute cholecystitis (AC) were discussed among global experts at the Tokyo Consensus Meeting held in 2006, and the first version of Tokyo Guidelines (TG07) was published in 2007 [1]. TG07 diagnostic criteria was revised in 2013 as Tokyo Guidelines 2013 (TG13) [2] in response to a validation study [3] of TG07. According to a validation survey [4] of TG13, the TG13 diagnostic criteria for acute cholecystitis (Table 5.1) had higher sensitivity and specificity than those of TG07, and continuous use of TG13 criteria was recommended in the updated version of Tokyo Guidelines (TG18) [5]. Regarding the severity grading system, while TG07 defined Grade III (severe) AC as AC with indication for emergent surgery, the revised TG13 described Grade III AC as AC associated with organ system dysfunction, which in some circumstances may require treatment in an intensive care unit [2]. According to a case series study of over 5000 patients, the prognosis for Grade III patients was significantly worse than that for Grades I and II [4]. The TG 13 severity grading of acute cholecystitis (Table 5.2) was recommended for continuous use in the TG18 severity grading of acute cholecystitis as a useful indicator from the perspective of predicting prognosis [5].

**Table 5.1** TG18/TG13 diagnostic criteria for acute cholecystitis. From [5], with permission

| |
|---|
| A. Local signs of inflammation |
| (1) Murphy's sign, (2) RUQ mass/pain/tenderness |
| B. Systemic signs of inflammation |
| (1) Fever, (2) elevated CRP, (3) elevated WBC count |
| C. Imaging findings characteristic of acute cholecystitis |
| Suspected diagnosis: one item in A + one item in B |
| Definite diagnosis: one item in A + one item in B + C |

## 5.2 Flowcharts for the Management of Acute Cholecystitis

### 5.2.1 Revisions of Flowcharts for the Management

Flowcharts for the management of acute cholecystitis (AC) were presented in TG07 [6] and revised in TG13 [7]. These flowcharts were useful to show recommended treatments according to the severity of AC. However, TG07 and TG13 did not cover issues like physical status, comorbidities, or other risk factors when choosing a treatment pathway according to severity. In

K. Mishima · G. Wakabayashi (✉)
Department of Surgery, Ageo Central General Hospital, Saitama, Japan
e-mail: gowaka@ach.or.jp


I. Di Carlo (ed.), *Difficult Acute Cholecystitis*, https://doi.org/10.1007/978-3-030-62102-5_5

addition, Grade III AC was considered not suitable for straightforward laparoscopic cholecystectomy (LC). In the TG18 guidelines [8], modified flowcharts (Figs. 5.1, 5.2, and 5.3) were proposed based on recent recommendations in the clinical setting and evidence reported after the publication of TG13 [9, 10]. The revision of flowcharts was aimed at improving the percentage of lives saved by allowing clinicians to determine how they can safely treat AC through the use of decision-making criteria even for severe cases.

**Table 5.2** TG18/TG13 severity grading for acute cholecystitis. From [5], with permission

| |
|---|
| Grade III (severe) acute cholecystitis is associated with dysfunction of any one of the following organs/systems: |
| 1. Cardiovascular dysfunction: hypotension requiring treatment with dopamine ≥5 μg/kg per min, or any dose of norepinephrine |
| 2. Neurological dysfunction: decreased level of consciousness |
| 3. Respiratory dysfunction: PaO2/FiO2 ratio < 300 |
| 4. Renal dysfunction: oliguria, creatinine >2.0 mg/dl |
| 5. Hepatic dysfunction: PT-INR >1.5 |
| 6. Hematological dysfunction: platelet count <100,000/mm$^3$ |
| Grade II (moderate) acute cholecystitis is associated with any one of the following conditions: |
| 1. Elevated WBC count (>18,000/mm$^3$) |
| 2. Palpable tender mass in the right upper abdominal quadrant |
| 3. Duration of complaints >72 ha |
| 4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis) |
| Grade I (mild) acute cholecystitis does not meet the criteria of Grade III or Grade II acute cholecystitis |

### 5.2.2 The Updated Version of Tokyo Guidelines (TG18)

The selection of treatment strategy for patients at each severity grade was based on risk factors [8]. The risk factors adopted in TG18 were: Charlson comorbidity index (CCI) score [9] and the American Society of Anesthesiologists physical status classification (ASA-PS) score [10]. Early LC to treat AC of moderate and severe grades (Grade II and III) should be performed only at advanced centers where experienced surgeons practice. An advanced center should have both appropriate personnel and facilities to manage the level of patients being managed. Surgeons should have experience in advanced laparoscopic techniques, and intensive care unit should be available. LC can be performed to treat AC if the conditions described above for each Grade are satisfied.

### 5.2.3 Definition of Early Cholecystectomy

TG07 recommended that surgery for AC be performed soon after hospital admission, whereas TG13 recommended that surgery be performed soon after admission and within 72 h after onset. When managing AC, it is difficult to determine precisely how many hours have passed since disease onset. The meta-analysis of the case study reports [11] found that compared with delayed cholecystectomy, early cholecystectomy for cases within 72 h of patient presentation or symptom onset was associated with lower mortality rates, complication rates, incidence of bile duct injury, and switching to open surgery.

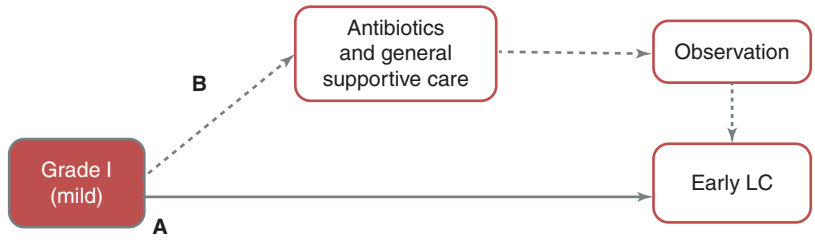


**Fig. 5.1** TG18 flowchart for the management of Grade I AC [8]. A, CCI 5 or less and/or ASA class II or less (low risk); B, CCI 6 or greater and/or ASA class III or greater (not low risk)

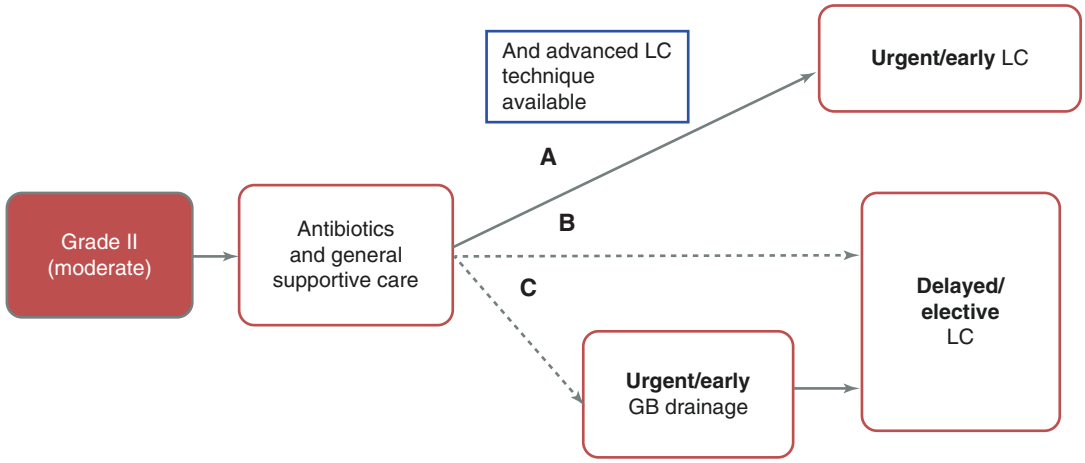


**Fig. 5.2** TG18 flowchart for the management of Grade II AC [8]. A, CCI 5 or less and/or ASA-PS class II or less (low risk); B, CCI 6 or greater and/or ASA-PS class III or greater (not low risk); C, antibiotics and general supportive care fail to control inflammation

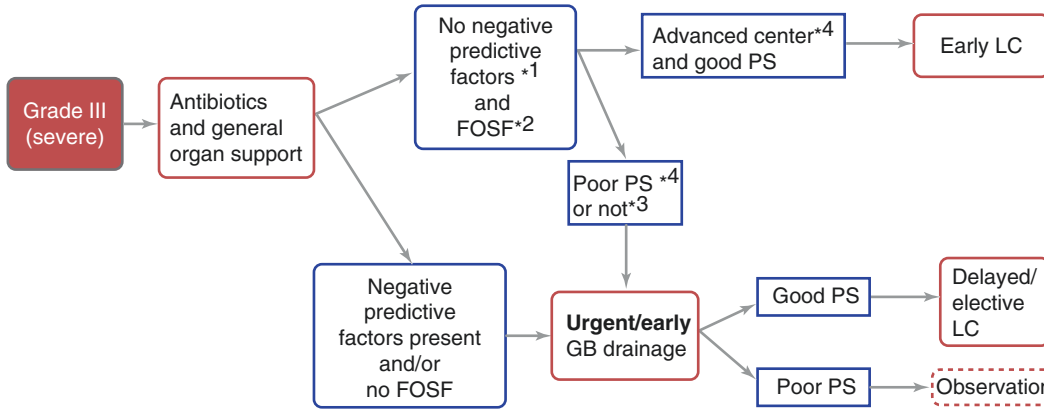


**Fig. 5.3** TG18 flowchart for the management of Grade III AC [8]. *1, negative predictive factors = jaundice (TBil ≥2), neurological dysfunction, respiratory dysfunction; *2, FOSF: favorable organ system failure = cardiovascular or renal organ system failure which is rapidly reversible after admission and before early LC in AC; *3, advanced center = intensive care and advanced laparoscopic techniques are available; *4, poor PS = CCI (Charlson comorbidity index) 4 or greater, ASA-PS 3 or greater

Similar results were also obtained with early cholecystectomy for cases with time from onset 72 h to 1 week [12, 13]. Therefore, TG 18 recommended early surgery regardless of exactly how much time has passed since onset, if a patient is deemed capable of withstanding surgery for AC.

## 5.3 Surgical Management of Acute Cholecystitis

Compared to TG13, TG18 recommended that clinicians should consider early LC even for moderate or severe AC [8]. The backbone of this change was the improvement of the operative skill for early

LC and perioperative care. Regarding the improvement in operative skills, standardized procedures of safe LC were proposed [14]. The critical view of safety (CVS) is the most important concept in the safe LC [15]. Several landmarks are helpful for surgeons to safely proceed surgical procedures during the process for the establishment CVS. The baseline of the segment 4 of the liver and the Rouviere's sulcus are good landmarks for the start line of dissecting the serosa of gallbladder for avoiding the bile duct injury of the anterior and posterior branch of Glissonian pedicles [14]. A bailout procedure should be chosen when a CVS cannot be achieved because of the presence of severe fibrosis.

## 5.4 Management Strategies for Gallbladder Drainage

A standard drainage method for surgically high-risk patients with AC and the latest developed endoscopic gallbladder drainage techniques were described in the updated Tokyo Guidelines 2018 (TG18) [16]. Percutaneous transhepatic gallbladder drainage (PTGBD) should be considered the first alternative to surgical intervention in surgically high-risk patients with AC. Also, endoscopic transpapillary gallbladder drainage or endoscopic ultrasound-guided gallbladder drainage can be considered in high-volume institutes by skilled endoscopists.

## 5.5 The Limits of TG18

### 5.5.1 Introduction

Tokyo Guidelines flowcharts allow clinicians to understand treatment flow at a glance and have proven useful standardization of the management of AC [8]. There have been significant changes in clinical management, including advances in surgical techniques [14] and equipment and progress in multidisciplinary treatment [16]. However, there are still issues warranting resolution.

### 5.5.2 Is Early LC Feasible for Patients with Grade III AC?

The severity grading of TG18/13 [5] is regarded as a useful classification system to predict the mortality rate of AC [4]. TG18 flowcharts [8] recommended that early LC or GB drainage following initial systemic treatment be performed for patients with Grade III AC. However, it is difficult for clinicians to choose early LC for Grade III AC according to TG18 flowchart, since the flowchart did not include elements of surgical difficulty and accompanying cholangitis. Although bailout procedures can be performed in difficult cases [14], conversion from LC to open surgery and postoperative complications are significantly more likely for patients at higher severity grades [17, 18]. A set of severity grading criteria including surgical difficulty is needed to be produced in the future.

### 5.5.3 How to Manage Elderly Patients with AC?

The management of elderly patients with AC is still a complex challenge due to the balance of benefits from LC versus the increased risk of perioperative morbidity and mortality [13]. In TG18 flowcharts [8], ASA-PS and age-adjusted CCI were adopted to evaluate physical status of patients, and age-adjusted CCI $\geq$6 and ASA-PS $\geq$3 were proposed as surgical risk factors based on the result of a cohort study [9]. Most elderly patients are classified into high-risk patients in this criteria. On the other hand, one study reported no deaths after cholecystectomy for patients with ASA-PS $\geq$3 at advanced centers [19]. In the era of aging society, AC in elderly patients is becoming an increasingly frequent problem. More case series data is needed to be gathered for future analysis to compare the clinical outcomes of early LC in high-risk elderly patients and those of conservative therapy with or without PTGBD.

### 5.5.4 What Determines the Advanced LC Technique?

In the 1990s, AC is regarded as contraindicated for LC according to SAGES guidelines [20]. But as times have changed, advances in optical and surgical devices and improvements in surgical techniques have led to the expansion of indications for LC [14]. As LC for AC has been more widely performed, vasculo-biliary injury is known to occur in a certain population of cases [21]. Therefore, TG18 flowcharts [8] recommended that early LC for AC be performed by surgeons with advanced techniques at advanced centers. In addition, the chapter of surgical management of AC was added to describe safe steps in LC for AC [14]. However, clinical evidence is scarce on advanced techniques of LC at the moment and warrants further investigation.

### 5.5.5 Summary

Based on studies that have found the lifespan of guidelines to be around 5 years [22], the Tokyo Guidelines Revision Committee revised the guidelines in 2013 and 2018. TG18 should be validated from abovementioned viewpoints during the next several years and be revised according to newly published clinical evidence.

## References


1. Hirota M, Takada T, Kawarada Y, Nimura Y, Miura F, Hirata K, et al. Diagnostic criteria and severity assessment of acute cholecystitis: Tokyo guidelines. J Hepatobiliary Pancreat Surg. 2007;14:78–82.
2. Yokoe M, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Gomi H, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2013;20:35–46.
3. Yokoe M, Takada T, Mayumi T, Yoshida M, Hasegawa H, Norimizu S, et al. Accuracy of the Tokyo guidelines for the diagnosis of acute cholangitis and cholecystitis taking into consideration the clinical practice pattern in Japan. J Hepatobiliary Pancreat Sci. 2011;18:250–7.
4. Yokoe M, Takada T, Hwang TL, Endo I, Akazawa K, Miura F, et al. Validation of TG13 severity grading in acute cholecystitis: Japan-Taiwan collaborative study for acute cholecystitis. J Hepatobiliary Pancreat Sci. 2017;24:338–45.
5. Yokoe M, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Gomi H, et al. Tokyo guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2018;25:41–54.
6. Miura F, Takada T, Kawarada Y, Nimura Y, Wada K, Hirota M, et al. Flowcharts for the diagnosis and treatment of acute cholangitis and cholecystitis: Tokyo guidelines. J Hepatobiliary Pancreat Surg. 2007;14:27–34.
7. Miura F, Takada T, Strasberg SM, Solomkin JS, Pitt HA, Gouma DJ, et al. TG13 flowchart for the management of acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2013;20:47–54.
8. Okamoto K, Takada T, Strasberg SM, Solomkin JS, Pitt HA, Gouma DJ, et al. Tokyo guidelines 2018: flowchart for the management of acute cholecystitis. J Hepatobiliary Pancreat Sci. 2018;25:55–72.
9. Endo I, Takada T, Hwang T-L, Akazawa K, Mori R, Miura F, et al. Optimal treatment strategy for acute cholecystitis based on predictive factors: Japan-Taiwan multicenter cohort study. J Hepatobiliary Pancreat Sci. 2017;24:346–61.
10. CholeS Study Group, West Midlands Research Collaborative. Population-based cohort study of variation in the use of emergency cholecystectomy for benign gallbladder diseases. Br J Surg. 2016;103:1716–26.
11. Cao AM, Eslick GD, Cox MR. Early laparoscopic cholecystectomy is superior to delayed acute cholecystitis: a meta-analysis of case–control studies. Surg Endosc. 2016;30:1172–82.
12. Ambe P, Weber SA, Christ H, Wassenberg D. Cholecystectomy for acute cholecystitis. How time-critical are the so called "golden 72 hours"? Or better "golden 24 hours" and "silver 25–72 hour"? A case control study. World J Emerg Surg. 2014;9:60.
13. Loozen CS, van Ramshorst B, van Santvoort HC, Boerma D. Early cholecystectomy for acute cholecystitis in the elderly population: a systematic review and meta-analysis. Dig Surg. 2017;34:371–9.
14. Wakabayashi G, Iwashita Y, Hibi T, Takada T, Strasberg SM, Asbun HJ, Endo I, et al. Tokyo guidelines 2018: surgical management of acute cholecystitis: safe steps in laparoscopic cholecystectomy for acute cholecystitis. J Hepatobiliary Pancreat Sci. 2018;25:73–86.
15. Strasberg SM, Hertl M, Soper NJ. An analysis of the problem of biliary injury during laparoscopic cholecystectomy. J Am Coll Surg. 1995;180:101–25.
16. Mori Y, Itoi T, Baron TH, Takada T, Strasberg SM, Pitt HA, Ukai T, et al. Tokyo guidelines 2018: management strategies for gallbladder drainage in patients with acute cholecystitis. J Hepatobiliary Pancreat Sci. 2018;25:87–95.
17. Asai K, Watanabe M, Kusachi S, Matsukiyo H, Saito T, Kodama H, et al. Risk factors for conversion of laparoscopic cholecystectomy to open surgery associ-

ated with the severity characteristics according to the Tokyo guidelines. Surg Today. 2014;44:2300–4.
18. Cheng WC, Chiu YC, Chuang CH, Chen CY. Assessing clinical outcomes of patients with acute calculous cholecystitis in addition to the Tokyo grading: a retrospective study. Kaohsiung J Med Sci. 2014;30:459–65.
19. Rodríguez-Sanjuán JC, Arruabarrena A, Sánchez-Moreno L, González-Sánchez F, Herrera LA, Gómez-Fleitas M. Acute cholecystitis in high surgical risk patients: percutaneous cholecystostomy or emergency cholecystectomy? Am J Surg. 2012;204:54–9.
20. The role of laparoscopic cholecystectomy (L.C.). Guidelines for clinical application. Society of American Gastrointestinal Endoscopic Surgeons (SAGES). Surg Endosc 1993;7:369–370
21. Tornqvist B, Waage A, Zheng Z, Ye W, Nilsson M. Severity of acute cholecystitis and risk of iatrogenic bile duct injury during cholecystectomy, a population-based case-control study. World J Surg. 2016;40:1060–7.
22. Shekelle PG, Ortiz E, Rhodes S, Morton SC, Eccles MP, Grimshaw JM, et al. Validity of the Agency for Healthcare Research and Quality clinical practice guidelines: how quickly do guidelines become outdated? JAMA. 2001;26:1461–7.