

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

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**Abstract** In 2007, the Tokyo Guidelines for the management of acute cholangitis and cholecystitis (TG07) were first published in the *Journal of Hepato-Biliary-Pancreatic Surgery*. The fundamental policy of TG07 was to achieve the objectives of TG07 through the development of consensus among specialists in this field throughout the world. Considering such a situation, validation and feedback from the clinicians' viewpoints were indispensable. What had been pointed out from clinical practice was the low diagnostic sensitivity of TG07 for acute cholangitis and the

presence of divergence between severity assessment and clinical judgment for acute cholangitis. In June 2010, we set up the Tokyo Guidelines Revision Committee for the revision of TG07 (TGRC) and started the validation of TG07. We also set up new diagnostic criteria and severity assessment criteria by retrospectively analyzing cases of acute cholangitis and cholecystitis, including cases of non-inflammatory biliary disease, collected from multiple institutions. TGRC held meetings a total of 35 times as well as international email exchanges with co-authors abroad. On June 9 and September 6, 2011, and on April 11,

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2012, we held three International Meetings for the Clinical Assessment and Revision of Tokyo Guidelines. Through these meetings, the final draft of the updated Tokyo Guidelines (TG13) was prepared on the basis of the evidence from retrospective multi-center analyses. To be specific, discussion took place involving the revised new diagnostic criteria, and the new severity assessment criteria, new flowcharts of the management of acute cholangitis and cholecystitis, recommended medical care for which new evidence had been added, new recommendations for gallbladder drainage and antimicrobial therapy, and the role of surgical intervention. Management bundles for acute cholangitis and cholecystitis were introduced for effective dissemination with the level of evidence and the grade of recommendations. GRADE systems were utilized to provide the level of evidence and the grade of recommendations. TG13 improved the diagnostic sensitivity for acute cholangitis and cholecystitis, and presented criteria with extremely low false positive rates adapted for clinical practice. Furthermore, severity assessment criteria adapted for clinical use, flowcharts, and many new diagnostic and therapeutic modalities were presented. The bundles for the management of acute cholangitis and cholecystitis are presented in a separate section in TG13.

Free full-text articles and a mobile application of TG13 are available via <http://www.jshbps.jp/en/guideline/tg13.html>.

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### Background before Tokyo Guidelines 2007

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

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

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

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

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

**Citation analysis 2007–2011 of TG07**

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

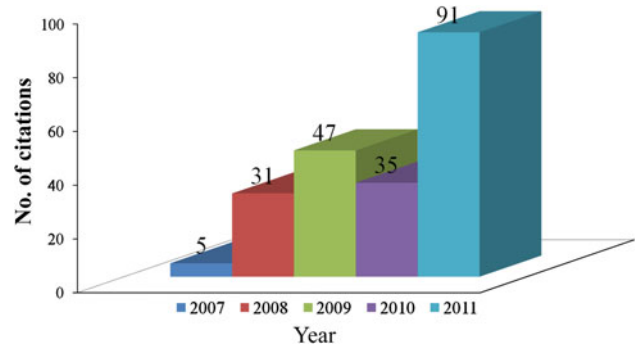
The results of the survey that examined the number of citations of TG07 until December 2011 show that the total number of citations of TG07 was 209 in 2009 (Table 1). The number of citations occurring each year since 2007 is presented in Fig. 1.

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

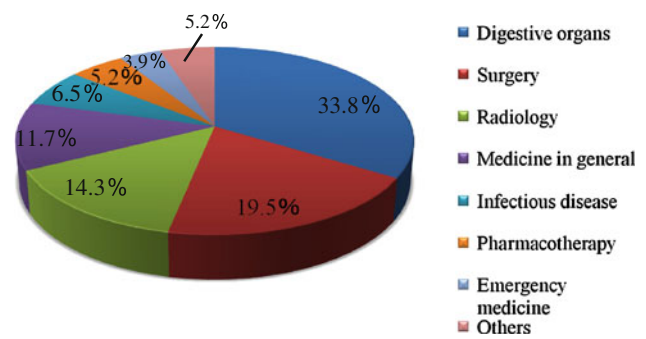
There were 112 treatises that had been cited from TG07. Figure 3 provides a breakdown of the residential areas of the authors. Table 2 shows the types of articles which cited TG07. Of the 76 original treatises, 20 (26.3 %) were cited in method sections (Fig. 4). The citation of original treatises in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

**Table 1** Summary of citations of TG07 (from January 2007 to December 2011)

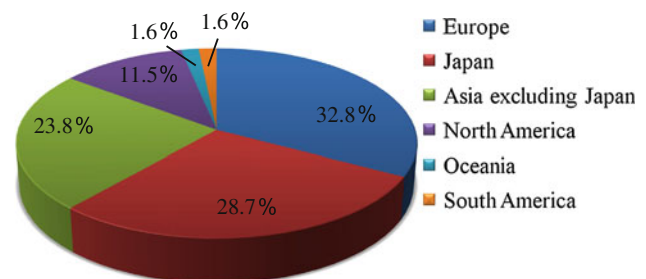
|  |     |
|--|-----|
| Number of papers in TG07 cited at least once                 | 14  |
| Total number of times of citation                            | 209 |
| Number of articles citing papers in TG07                     | 122 |
| Number of journals publishing articles citing papers in TG07 | 77  |



**Fig. 1** Annual number of citations of TG07



**Fig. 2** Categories of the journals publishing articles citing papers in TG07 (n = 77)



**Fig. 3** Geographical origin of authors citing papers in TG07 (n = 122)

**Need for revision of TG07**

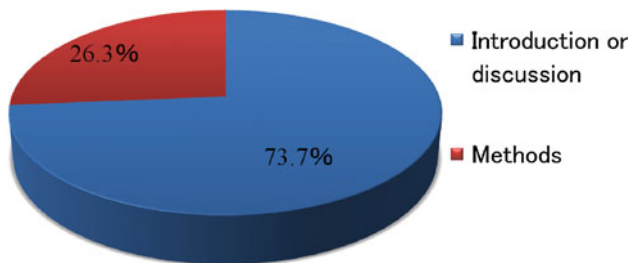
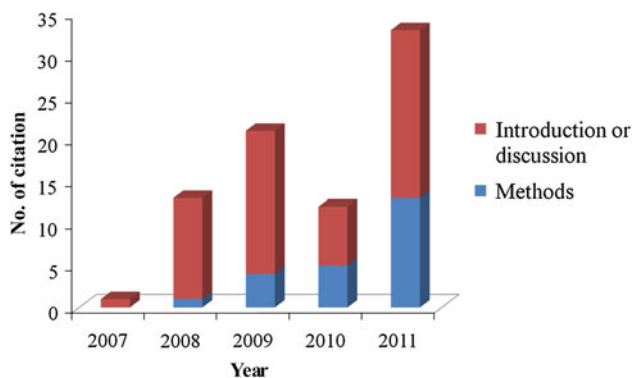
1. The development of evidence-based guidelines, clinical practice and assessment

The publication of TG07 enabled the presentation of the first international diagnostic criteria and severity assessment

**Table 2** Types of articles citing TG07

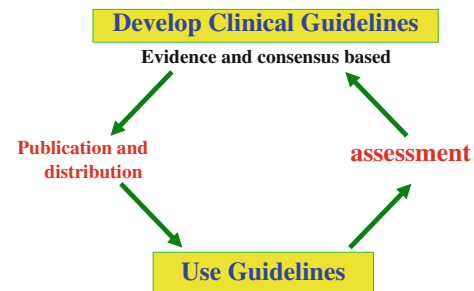
| Types of articles | No. of articles |
|-------------------|-----------------|
| Original article  | 76 (62.3 %)     |
| Review            | 20 (16.4 %)     |
| Case report       | 11 (9.0 %)      |
| Guideline         | 7 (5.7 %)       |
| Others            | 8 (6.6 %)       |
| Total             | 122             |

In 17 articles, patients were diagnosed according to the diagnostic criteria and severity assessment of TG.

**Fig. 4** Section where cited in original articles ( $n = 76$ )**Fig. 5** Annual number of original articles citing papers in TG07

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

In general, following the publication of clinical practice guidelines, new findings are reported concerning diagnosis

**Fig. 6** Evidence–practice cycle

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

## 2. Validity of TG07

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

## Process of the development of Tokyo Guidelines 2013 (TG13)

### 1. The First International Meeting for the development of TG13

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

### 2. The Second International Meeting for the development of TG13

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

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

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

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

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

6. Third International Meeting for the development of TG13

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

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

## The GRADE systems

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

In the assessment of the quality of evidence, the level of evidence is classified as “high” (level A), “moderate” (level B), “low” (level C), or “very low” (level D). A randomized trial is, in general, classified as having high-level evidence. However, due to limitations in each study,

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

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

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

## Introduction of bundles for the management of acute cholangitis and cholecystitis

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



**Fig. 7** GRADE system (quality of evidence) [15–17]

| Initial quality of evidence | Study design   | Lower if   | Higher if   |
|-----------------------------|--|--|---|
| High                        | RCT, systematic review, meta-analysis                  | Study limitations:<br>1↓ Serious<br>2↓ Very serious  | Magnitude of effect:<br>2↑ Very strong<br>1↑ Strong           |
| Moderate                    |  | Inconsistency:<br>1↓ Serious<br>2↓ Very serious  | Dose-response gradient<br>1↑                                  |
| Low                         | Observational study (cohort study, case control study) | Indirectness:<br>1↓ Serious<br>2↓ Very serious   | All plausible confounders would have reduced the effect<br>1↑ |
| Very low                    | Any other evidence (case series, case study)           | Impression:<br>1↓ Serious<br>2↓ Very serious<br>Publication bias<br>1 likely<br>2↓ Very likely |   |

Definition: Overall quality of evidence across studies for the outcome

level A : 「High」 level B : 「Moderate」 level C : 「Low」 level D : 「Very low」

#### 1. How to judge a Grade of recommendation

Totally judgment with evidence, harm and benefit

- ① Level of evidence A, B, C, D
- ② Patient's preference Yes, No
- ③ Harm and benefit Yes, No
- ④ Cost effectiveness Yes, No

#### 2. How to show a Grade of recommendation : 2 steps

Recommendation 1: Strong recommendation (Do it, Don't do it):

Over 70% of clinical practitioners will agree  
= 「We recommend」

Recommendation 2: Weak recommendation (probably do it, probably don't do it):

Less than 70% will agree = 「We suggest」

**Fig. 8** GRADE system (grade of recommendation) [15–17]

the guidelines and to provide guidelines for conducting a survey concerning changes in medical care before and after publication of TG13.

## Summary

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

**Conflict of interest** None.

## References

- Takada T, Kawarada Y, Nimura Y, Yoshida M, Mayumi T, Sekimoto M, et al. Background: Tokyo Guidelines for the management of acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Surg.* 2007;14:1–10.
- Tokyo Guidelines for the management of acute cholangitis and cholecystitis. Proceedings of a consensus meeting, April 2006, Tokyo, Japan. *J Hepato-Biliary Pancreat Surg.* 2007;14:1–121.
- 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.
- Wada K, Takada T, Kawarada Y, Nimura Y, Miura F, Yoshida M, et al. Diagnostic criteria and severity assessment of acute cholangitis: Tokyo guidelines. *J Hepatobiliary Pancreat Surg.* 2007;14:52–8.
- 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.
- Strasberg SM. Acute calculous cholecystitis. *N Engl J Med.* 2008;358:2804–11.
- Cameron JL, Cameron AM. Current surgical therapy. 10th ed. Elsevier Mosby: Philadelphia. 2011; p. 345–348.
- Dooley JS, Lok A, Burroughs A, Heathcote J. *Sherlock's diseases of the liver and biliary system*, 12th ed. Blackwell: Hoboken; 2011.
- Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clinical Infect Dis.* 2010;50(2):133–64.
- Murata A, Matsuda S, Kuwabara K, Fujino Y, Kubo T, et al. Evaluation of compliance with the Tokyo Guidelines for the management of acute cholangitis based on the Japanese administrative database associated with the Diagnosis Procedure Combination system. *J Hepatobiliary Pancreat Sci.* 2010;18:53–9.
- Yokoe M, Takada T, Mayumi T, Yoshida M, Hasegawa H, Norimizo 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.
12. Shekelle PG, Ortiz E, Rhodes S, Morton SC, Eccles MP, Grimshaw JM, Woolf SH. Validity of the Agency for Healthcare Research and Quality clinical practice guidelines: how quickly do guidelines become outdated? *JAMA.* 2001;286:1461–7.
  13. Kiriya S, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Pitt HA, et al. New diagnostic criteria and severity assessment of acute cholangitis in revised Tokyo guidelines. *J Hepatobiliary Pancreat Sci.* 2012;19:548–56.
  14. Yokoe M, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Gomi H, et al. New diagnostic criteria and severity assessment of acute cholecystitis in revised Tokyo guidelines. *J Hepatobiliary Pancreat Sci.* 2012;19:578–85.
  15. Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches. The GRADE Working Group. *BMC Health Serv Res.* 2004; 4(1):38.
  16. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. Rating quality of evidence and strength of recommendations. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336:924–6.
  17. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ, et al. Rating quality of evidence and strength of recommendations. What is “quality of evidence” and why is it important to clinicians? *BMJ.* 2008;336:995–8.