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New diagnostic criteria and severity assessment of acute cholangitis in revised Tokyo guidelines

Seiki Kiriyama · Tadaihiro Takada · Steven M. Strasberg · Joseph S. Solomkin · Toshihiko Mayumi · Henry A. Pitt · Dirk J. Gouma · O. James Garden · Markus W. Büchler · Masamichi Yokoe · Yasutoshi Kimura · Toshio Tsuyuguchi · Takao Itoi · Masahiro Yoshida · Fumihiko Miura · Yuichi Yamashita · Kohji Okamoto · Toshifumi Gabata · Jiro Hata · Ryota Higuchi · John A. Windsor · Philippus C. Bornman · Sheung-Tat Fan · Harijt Singh · Eduardo de Santibanes · Harumi Gomi · Shinya Kusachi · Atsuhiko Murata · Xiao-Ping Chen · Palepu Jagannath · SungGyu Lee · Robert Padbury · Miin-Fu Chen

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Abstract

Background The Tokyo Guidelines for the management of acute cholangitis and cholecystitis were published in 2007 (TG07) and have been widely cited in the world literature. Because of new information that has been published since 2007, we organized the Tokyo Guidelines Revision Committee to conduct a multicenter analysis to develop the updated Tokyo Guidelines (TG13).

Methods/materials We retrospectively analyzed 1,432 biliary disease cases where acute cholangitis was suspected. The cases were collected from multiple tertiary care centers in Japan. The ‘gold standard’ for acute cholangitis in this study was that one of the three following conditions was present: (1) purulent bile was observed; (2) clinical remission following bile duct drainage; or (3) remission was achieved by antibacterial therapy alone, in

S. Kiriyama (✉)

Department of Gastroenterology, Ogaki Municipal Hospital,
4-86 Minaminokawa-cho, Ogaki, Gifu 503-8502, Japan
e-mail: skiriya@ip.mirai.ne.jp

T. Takada · F. Miura

Department of Surgery, Teikyo University School of Medicine,
Tokyo, Japan

S. M. Strasberg

Section of Hepatobiliary and Pancreatic Surgery,
Washington University in Saint Louis School of Medicine,
Saint Louis, MO, USA

J. S. Solomkin

Department of Surgery, University of Cincinnati College
of Medicine, Cincinnati, OH, USA

T. Mayumi

Department of Emergency and Critical Care Medicine,
Ichinomiya Municipal Hospital, Ichinomiya, Japan

H. A. Pitt

Department of Surgery, Indiana University School of Medicine,
Indianapolis, IN, USA

D. J. Gouma

Department of Surgery, Academic Medical Center,
Amsterdam, The Netherlands

O. J. Garden

Clinical Surgery, The University of Edinburgh, Edinburgh, UK

M. W. Büchler

Department of Surgery, University of Heidelberg,
Heidelberg, Germany

M. Yokoe

General Internal Medicine, Nagoya Daini Red Cross Hospital,
Nagoya, Japan

Y. Kimura

Department of Surgical Oncology and Gastroenterological
Surgery, Sapporo Medical University School of Medicine,
Sapporo, Japan

T. Tsuyuguchi

Department of Medicine and Clinical Oncology, Graduate
School of Medicine Chiba University, Chiba, Japan

T. Itoi

Department of Gastroenterology and Hepatology,
Tokyo Medical University, Tokyo, Japan

M. Yoshida

Clinical Research Center Kaken Hospital, International
University of Health and Welfare, Ichikawa, Japan

Y. Yamashita

Department of Gastroenterological Surgery, Fukuoka University
School of Medicine, Fukuoka, Japan

K. Okamoto

Department of Surgery, Kitakyushu Municipal Yahata Hospital,
Kitakyushu, Japan

patients in whom the only site of infection was the biliary tree. Comparisons were made for the validity of each diagnostic criterion among TG13, TG07 and Charcot's triad.

Results The major changes in diagnostic criteria of TG07 were re-arrangement of the diagnostic items and exclusion of abdominal pain from the diagnostic list. The sensitivity improved from 82.8 % (TG07) to 91.8 % (TG13). While the specificity was similar to TG07, the false positive rate in cases of acute cholecystitis was reduced from 15.5 to 5.9 %. The sensitivity of Charcot's triad was only 26.4 % but the specificity was 95.6 %. However, the false positive rate in cases of acute cholecystitis was 11.9 % and not negligible. As for severity grading, Grade II (moderate) acute cholangitis is defined as being associated with any two of the significant prognostic factors which were derived from evidence presented recently in the literature. The factors chosen allow severity assessment to be performed soon after diagnosis of acute cholangitis.

Conclusion TG13 present a new standard for the diagnosis, severity grading, and management of acute cholangitis.

Keywords Acute cholangitis · Biliary infection · Diagnostic criteria · Severity assessment · Charcot's triad

T. Gabata

Department of Radiology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan

J. Hata

Department of Endoscopy and Ultrasound, Kawasaki Medical School, Okayama, Japan

R. Higuchi

Department of Surgery, Institute of Gastroenterology Tokyo Women's Medical University, Tokyo, Japan

J. A. Windsor

Department of Surgery, The University of Auckland, Auckland, New Zealand

P. C. Bornman

Division of General Surgery, Health Sciences, University of Cape Town, Cape Town, South Africa

S.-T. Fan

Department of Surgery, Queen Mary Hospital, The University of Hong Kong, Hong Kong, Hong Kong

H. Singh

Department of Hepato-Pancreato-Biliary Surgery, Hospital Selayang, Batu caves, Malaysia

E. de Santibanes

Department of Surgery, Hospital Italiano, University of Buenos Aires, Buenos Aires, Argentina

H. Gomi

Center for Clinical Infectious Diseases, Jichi Medical University, Tochigi, Japan

Introduction

Patients with acute cholangitis are at risk for developing severe infection that can be fatal unless appropriate medical care is provided at an early stage. Advances in antibiotic therapy and acute care as well as a wide diffusion of expertise in biliary endoscopy have resulted in reduction of morbidity and mortality from acute cholangitis. However, it remains a life-threatening disease and early determination of disease severity is essential to select appropriate therapy, particularly the timing of biliary decompression. In 2007, we conducted a systematic review and sponsored an international consensus conference in Tokyo. This meeting resulted in the introduction of the new Tokyo Guidelines (TG07) for diagnosis and severity assessment of acute cholangitis [1].

Diagnostic and severity assessment criteria need to be updated periodically based on new information, criticisms, and suggestions for improvement. For instance, ever since Charcot reported a patient with severe acute cholangitis as a case of 'hepatic fever' in 1877, Charcot's triad has been widely considered to be one of the most important diagnostic criteria [2–6]. However, Charcot's triad has extremely low sensitivity despite its high specificity. In addition,

S. Kusachi

Department of Surgery, Toho University Medical Center Ohashi Hospital, Tokyo, Japan

A. Murata

Department of Preventive Medicine and Community Health, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

X.-P. Chen

Department of Surgery, Hepatic Surgery Centre, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

P. Jagannath

Department of Surgical Oncology, Lilavati Hospital and Research Centre, Mumbai, India

S. Lee

HepatoBiliary Surgery and Liver Transplantation, Asan Medical Center, Ulsan University, Ulsan, Korea

R. Padbury

Division of Surgical and Specialty Services, Flinders Medical Centre, Bedford Park, Australia

M.-F. Chen

Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan

false positive cases of acute cholecystitis are not unusual with this classic diagnostic triad.

With experience we and others found potential shortcomings in TG07 [7]. Consequently, the Tokyo Guidelines Revision Committee was assembled and gathered a large number of cases of acute cholangitis from tertiary care centers in Japan. These cases acted as a gold standard to assess diagnostic and severity criteria such as TG07. The present study has confirmed limitations of TG07 and presents updated TG13 criteria which have improved sensitivity and specificity and which importantly, unlike the criteria in TG07, allow severity assessment at the time of presentation so that biliary drainage or other procedures can be performed without delay.

Methods

In the present multicenter study, 1,432 patients were enrolled with biliary tract abnormalities and suspected acute cholangitis between January 2007 and July 2011. Choledocholithiasis or biliary stricture was confirmed by direct cholangiography (i.e., endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography). Acute cholecystitis was confirmed by pathologic examination of excised gallbladders.

The establishment of guidelines for diagnosis and severity assessment in a disease requires that there is diagnostic certainty by which to assess criteria. For acute cholecystitis this may be provided by pathologic examination of excised gallbladders; however, pathologic specimens are not available in acute cholangitis. Our approach in this study was to

Table 1 Clinical characteristics of patients

	Acute cholangitis (<i>n</i> = 794) ^a	Other disease (<i>n</i> = 638)
Etiology;		Choledocholithiasis (<i>n</i> = 178),
choledocholithiasis	(<i>n</i> = 402)	obstructive jaundice caused by
malignant tumor	(<i>n</i> = 392)	acute cholecystitis (<i>n</i> = 219)
Age	71.7 ± 11.8	68.5 ± 12.3
Sex	490:304	307:331
(male:female)		
Charcot triad	147 (18.5 %)	26 (4.1 %)
Abdominal	435 (54.8 %)	309 (48.4 %)
pain		
Presence of purulent biliary leakage		
Clinical remission due to bile duct drainage		
Remission achieved by antimicrobial therapy alone in patients in whom the only site of infection was the biliary tree		

^a The ‘Gold Standard’ for acute cholangitis in this study was that one of the following three conditions was present

gather data from 794 patients who were considered to have had acute cholangitis based on one of the following three criteria: (1) presence of purulent biliary leakage; (2) clinical remission due to bile duct drainage; or (3) remission achieved by antimicrobial therapy alone in patients in whom the only site of infection was the biliary tree. For comparison we also gathered data from 638 patients who had other biliary tract abnormalities (Table 1).

Using these patients, we adjusted diagnostic criteria to have the highest sensitivity and specificity for acute cholangitis. For establishment of new severity assessment criteria, we examined variables reported in the literature either as predictive of poor prognosis in acute cholangitis or of need for urgent biliary drainage (Table 2). These

Table 2 Prognostic factors in acute cholangitis

Prognostic factor	Positive value	References
Hyperbilirubinemia	>2 mg/dL	[8]
	>2.2 mg/dL	[9]
	>2.93 mg/dL	[10]
	>4 mg/dL	[11, 12]
	>5.26 mg/dL	[13]
	>5.56 mg/dL	[14]
	>8.1 mg/dL, >9.2 mg/dL	[15]
	>9.1 mg/dL	[16]
	>10 mg/dL	[17]
	Hypoalbuminemia	<3.0 g/dL
Acute renal failure		[8, 9, 11, 19, 20]
	BUN (>20–>64 mg/dL)	
	Creatinine (>1.5–>2.0 mg/dL)	
Shock		[8, 12, 13, 19]
Reduced platelet count	<1,00,000–<1,50,000/mm ³	[13, 18, 20]
Endotoxemia/bacteremia		[9, 10, 14, 20]
High fever	>38 °C	[8]
	>39 °C	[12]
	>40 °C	[16]
Medical comorbidity		[8, 11, 13, 18, 19]
Elderly patient	≥50 years old	[11]
	≥60 years old	[8]
	≥70 years old	[19, 21]
	≥75 years old	[22]
Malignancy as etiology		[9, 11, 14]
Prolonged prothrombin time	≤14 s	[10, 22]
	≤15 s	[8]
Leukocytosis	≤12,000	[8]
	≤20,000	[16, 17]
Current smoking	Yes	[21, 22]

variables were then used to construct a grading system that would permit determination of the level of severity at the time of diagnosis so that those patients who need urgent biliary decompression could receive treatment without delay.

For confirming the advantage of these revisions, updated diagnostic criteria and severity assessment criteria also were retrospectively assessed by the present multicenter analysis.

Results

Formulation of new diagnostic criteria for acute cholangitis

Assessment of Charcot's triad and TG07 diagnostic criteria for acute cholangitis

Analysis of the 1,432 cases of biliary tract diseases showed that Charcot's triad had low sensitivity (26.4 %) but high specificity (95.9 %) for acute cholangitis, with 11.9 % of cases of acute cholecystitis demonstrating Charcot's triad. On the other hand, the sensitivity and specificity of TG07 diagnostic criteria were 82.6 and 79.8 %, respectively, while 11.9 % of cases acute cholecystitis would have fit the diagnostic criteria for acute cholangitis if TG07 criteria were applied (Table 3). Furthermore, TG07 diagnostic criteria for acute cholangitis were found to have insufficient sensitivity for making an early diagnosis of life-threatening acute cholangitis.

Revision of TG07 diagnostic criteria for acute cholangitis

It seemed that the shortcomings of TG07 might be related to inappropriate combination of such items as clinical context and manifestations, laboratory data and imaging findings. Therefore, for TG13, categories of

diagnostic items were constructed based on the three main clinical manifestations used in the diagnosis of acute cholangitis: (a) fever and/or evidence of inflammatory response, (b) jaundice and abnormal liver function tests, and (c) abdominal pain, a history of biliary diseases, biliary dilatation, or other biliary manifestations. The presence of a finding in all three of these categories has been considered to be diagnostic of acute cholangitis.

Abdominal pain and a history of biliary tract disease, however, are also common indicators of other biliary problems such as acute cholecystitis and even acute hepatitis. Acute cholecystitis application of the first draft criteria of TG13 (which included abdominal pain and a history of biliary tract disease) to patients with acute cholecystitis resulted in 38.8 % of patients with acute cholecystitis meeting the criteria for diagnosis of acute cholangitis. However, despite a high sensitivity for acute cholangitis of 95.1 % for these diagnostic criteria the specificity of (66.3 %) was disappointingly low (Table 3). In the next iteration of the diagnostic criteria, abdominal pain and the history of biliary diseases were deleted from the diagnostic criteria. This resulted in the best outcome in terms of high sensitivity and specificity for acute cholangitis and low false positive rate for acute cholecystitis (Table 3) and these were the diagnostic criteria which were adopted for TG13 (Table 3).

The final TG13 diagnostic criteria are shown in Table 4. To make a definitive diagnosis one item from each of the three categories (A–C) is required. Furthermore, a 'suspected' diagnosis can be made when there is one item present from the A list and one item from either the B or C list. By establishing 'suspected diagnosis', early biliary drainage or source control of infection among patients with acute cholangitis can be provided without waiting for a definitive diagnosis.

One of the items in category A involves determination of the presence of abnormal laboratory tests. Thresholds for declaring positivity test might be set at the upper limit of normal for the tests. The disadvantage of this approach is that minor abnormalities in the tests are not uncommon in acute cholecystitis. Therefore, a somewhat higher threshold for acute cholangitis is desirable. The normal upper limit range of the liver function tests differs from facility to facility. Therefore, a fixed threshold is not practical. Instead, the threshold was set at 1.5 times the upper limit of normal in a facility. We then conducted a multicenter analysis to compare this threshold with two other types of threshold in terms of the diagnostic ability for acute cholangitis. When the threshold was set at 1.5 times the upper limit, both sensitivity and specificity were similar to those at which another two types of threshold were applied

Table 3 Retrospective comparison of various diagnostic criteria of acute cholangitis in a multicenter study in Japan

	Charcot's triad (%)	TG07 (%)	The first draft criteria (with abdominal pain and history of biliary disease) (%)	TG13 (%)
Sensitivity	26.4	82.6	95.1	91.8
Specificity	95.9	79.8	66.3	77.7
Positive rate in acute cholecystitis	11.9	15.5	38.8	5.9

Table 4 TG13 Diagnostic criteria for acute cholangitis

A. Systemic inflammation

A-1. Fever and/or shaking chills

A-2. Laboratory data: evidence of inflammatory response

B. Cholestasis

B-1. Jaundice

B-2. Laboratory data: abnormal liver function tests

C. Imaging

C-1. Biliary dilatation

C-2. Evidence of the etiology on imaging (stricture, stone, stent, etc.)

Suspected diagnosis: one item in A + one item in either B or C

Definite diagnosis: one item in A, one item in B and one item in C

A-2 Abnormal white blood cell counts, increase of serum C-reactive protein levels, and other changes indicating inflammation

B-2 Increased serum ALP, r-GTP (GGT), AST, and ALT levels

Thresholds

A-1	Fever		BT >38 °C
A-2	Evidence of inflammatory response	WBC ($\times 1,000/\mu\text{L}$)	<4, or >10
		CRP (mg/dL)	≥ 1
B-1	Jaundice		T-Bil ≥ 2 (mg/dL)
B-2	Abnormal liver function tests	ALP (IU)	$>1.5 \times \text{STD}^*$
		γ GTP (IU)	$>1.5 \times \text{STD}^*$
		AST (IU)	$>1.5 \times \text{STD}^*$
		ALT (IU)	$>1.5 \times \text{STD}^*$

Other factors which are helpful in diagnosis of acute cholangitis include abdominal pain (Right upper quadrant (RUQ) or upper abdominal) and a history of biliary disease such as gallstones, previous biliary procedures, and placement of a biliary stent

In acute hepatitis, marked systematic inflammatory response is observed infrequently. Virological and serological tests are required when differential diagnosis is difficult

ALP Alkaline phosphatase, r-GTP (GGT) r-glutamyltransferase,

AST aspartate aminotransferase, ALT alanine aminotransferase

* *STD* upper limit of normal value

Table 5 Comparisons of various cut-offs for laboratory testing results for the diagnosis of acute cholangitis in Japan

	Thresholds for positivity of test		
	Adoption	Limit of this test (low)	Limit of this test (high)
T-Bil (mg/dL)	≥ 2	Same	Same
ALP (IU)	$>1.5 \times \text{STD}$	≥ 400	≥ 500
γ GTP (IU)	$>1.5 \times \text{STD}$	≥ 100	≥ 150
AST (IU)	$>1.5 \times \text{STD}$	≥ 50	≥ 100
ALT (IU)	$>1.5 \times \text{STD}$	≥ 50	≥ 100
WBC ($\times 1,000/\mu\text{L}$)	<4, or >10	Same	Same
CRP (mg/dL)	≥ 1	Same	Same
BT	>38 °C	Same	Same
Sensitivity	91.8 %	93.0 %	92.7 %
Specificity	77.7 %	77.9 %	77.9 %
Positive rate in acute cholecystitis ($n = 219$)	5.9 %	9.1 %	8.7 %

STD upper limit of normal value

(Table 5). From the above results, it was considered appropriate and practical that the threshold was set at 1.5 times the normal upper limit for the liver function test in the particular facility.

Formulation of new severity assessment criteria for acute cholangitis

Assessment of TG07 severity assessment criteria for acute cholangitis

The use of TG07 severity assessment criteria in actual clinical situations has shown that use of these criteria was

Table 6 Timing of biliary drainage among patients with acute cholangitis diagnosed with TG07—multicenter analysis of acute cholangitis for revision of TG07 severity criteria of acute cholangitis

Timing of drainage/ treatment for etiology	Grade III	Grade II	Grade I	Total
Within 24 h	41	258 (Grade II or I)		297
24–48 h	9	54	0	63
After 48 h	20	130	12	162
Drainage (–)	2	3	96	101
Total	72 (11.6 %)	551 (88.4 %) (Grade II or I)		623

inefficient in separating moderate cases (Grade II) from mild cases (Grade I) at the time of initial diagnosis. In TG07, Grades II and I were only assessed after observation of the initial treatment courses. In this treatment strategy, urgent biliary drainage can be indicated for cases assessed as ‘severe’, but provision of early biliary drainage is impossible for cases as ‘moderate’. The present multicenter analysis showed that many cases (46.8 %, 258 of 551 cases) of Grade II or I underwent urgent biliary drainage in the same manner as Grade III. In these cases, differentiation between grade II and Grade I was impossible, because the definition of Grade II in TG07 was ambiguous (Table 6).

Revision of TG07 severity assessment criteria for acute cholangitis

Given these insufficiencies of TG07 in clinical practice, a revision was sought which might improve severity assessment strategies upon diagnosis in order to allow selection of those patients who needed immediate source control of infection. Since there had been no scientifically based definitions of ‘moderate cases’ except for the consensus-based TG07 we needed a new definition of what constituted moderate cases needing early source control in TG13.

To improve TG07 we examined items reported as predictive factors of poor prognosis among patients with acute

Table 7 TG13 Severity assessment criteria for acute cholangitis

Grade III (Severe) acute cholangitis	
‘Grade III’ acute cholangitis is defined as acute cholangitis that is associated with the onset of dysfunction at least in any one of the following organs/systems	
1. Cardiovascular dysfunction	Hypotension requiring dopamine $\geq 5 \mu\text{g/kg}$ per min, or any dose of norepinephrine
2. Neurological dysfunction	Disturbance of consciousness
3. Respiratory dysfunction	$\text{PaO}_2/\text{FiO}_2$ ratio < 300
4. Renal dysfunction	Oliguria, serum creatinine $> 2.0 \text{ mg/dL}$
5. Hepatic dysfunction	PT-INR > 1.5
6. Hematological dysfunction	Platelet count $< 1,00,000/\text{mm}^3$
Grade II (moderate) acute cholangitis	
‘Grade II’ acute cholangitis is associated with any two of the following conditions:	
1. Abnormal WBC count ($> 12,000/\text{mm}^3$, $< 4,000/\text{mm}^3$)	
2. High fever ($\geq 39^\circ\text{C}$)	
3. Age (≥ 75 years)	
4. Hyperbilirubinemia (total bilirubin $\geq 5 \text{ mg/dL}$)	
5. Hypoalbuminemia ($< \text{STD} \times 0.7$)	
Grade I (mild) acute cholangitis	
‘Grade I’ acute cholangitis does not meet the criteria of ‘Grade III (severe)’ or ‘Grade II (moderate)’ acute cholangitis at initial diagnosis	

Early diagnosis, early biliary drainage and/or treatment for etiology, and antimicrobial administration are fundamental treatment for acute cholangitis classified not only ‘Grade III (severe)’ and ‘Grade II (moderate)’ but also Grade I (mild)

Therefore, it is recommended that patients with acute cholangitis who do not respond to the initial medical treatment (general supportive care and antimicrobial therapy) undergo early biliary drainage or treatment for etiology

STD lower limit of normal value

Table 8 Timing of biliary drainage among patients with acute cholangitis diagnosed with TG13—multicenter analysis of acute cholangitis for revision of TG07 Severity assessment criteria for acute cholangitis

Timing of drainage/treatment for etiology	Grade III	Grade II	Grade I	Total
Within 24 h	41	116	140 (135)	297
24–48 h	9	13	41 (41)	63
After 48 h	20	48	94	162
Drainage (–)	2	39	60	101
Total	72 (11.6 %)	216 (34.7 %)	335 (53.8 %)	623

() indicates the number of cases that have early drainage and treatment of etiology

Table 9 TG13 Severity assessment criteria and Charcot's triad

Severity grading of TG13	Charcot's triad	
	Yes (<i>n</i> = 110)	No (<i>n</i> = 513)
Grade III	13 (11.8 %)	59 (11.5 %)
Grade II	52 (47.3 %)	164 (32.0 %)
Grade I	45 (40.9 %)	290 (56.5 %)

cholangitis and factors associated with the need for urgent biliary drainage (Table 2). Furthermore, factors that endoscopic gastroenterologists value in determining the timing of biliary drainage were integrated except for the factors that define Grade III cases (severe cases). Presence or absence of endotoxemia and/or bacteremia, and malignancy as etiology cannot be assessed upon the diagnosis of acute cholangitis and were therefore not included. Medical comorbidities such as diabetes mellitus and neurological diseases were considered as severity factors; however, due to their wide disease spectrum, it was decided that it was impractical to include co-morbidity in TG13. The criteria selected for moderate severity were leukocytosis high fever, age >75 years, hyperbilirubinemia, and hypoalbuminemia. The presence of any two of the five positive criteria will classify the disease as Grade II (moderate).

The revised assessment criteria for acute cholangitis are shown in Table 7.

Assessment of TG13 severity assessment criteria for acute cholangitis

We performed a multicenter analysis using the TG13 severity assessment criteria for acute cholangitis in real clinical settings. Of the 623 cases of acute cholangitis where severity grading was retrospectively made clear, there were 72 Grade III cases (11.6 %), 216 Grade II cases (34.7 %) and 335 Grade I cases (53.8 %). Furthermore, the Grade II cases requiring urgent or early biliary drainage accounted for 46 % of the acute cholangitis cases. An examination of Grade I cases where biliary drainage had

been carried out within 24 h and within 48 h found 140 cases (41.8 %) and 181 cases (54.0 %), respectively. It was surprising that so many patients with Grade I criteria had undergone biliary drainage. However, on further analysis it was found that almost all Grade I cases that had undergone early biliary drainage were due to biliary obstruction such as common duct stones. These types of interventions accounted for 135 of 140 cases (94.8 %) within 24 h and 41 cases (100 %) within 48 h, respectively. The number of Grade I cases that had undergone biliary drainage as an urgent treatment to control infection were small (Table 8).

Of the 110 cases of acute cholangitis that met the Charcot's triad, 13 cases (11.8 %) have been classified as Grade III, and 52 as Grade II (47.3 %), respectively. Furthermore, approximately 80 % (59 of 72 cases) of Grade III cases in TG13 failed to satisfy Charcot's triad (Table 9). Charcot's triad was not found to be associated with disease severity.

Discussion

The main goals of diagnostic and severity assessment criteria are to allow early establishment of diagnosis and selection of the most appropriate management plan for the stage of the disease. This was attempted for acute cholangitis in TG07 where the guidelines were based on available literature and input of experts at a consensus conference held in Tokyo in 2006. At that meeting, diagnostic criteria were presented combining blood tests and diagnostic imaging together with Charcot's triad [23]. However, there is a report showing that the sensitivity was low (63.9 %) for making a definite diagnosis of acute cholangitis [7]. It is well established that guidelines need periodic assessment and revision; however, in the case of TG07 this was particularly so because of shortcomings that became evident through application in clinical practice and as a result of new information in the literature. As in TG07, initial iterations were produced in Japan with modifications incorporating the input of experts from around the world.

A particularly vexing problem in studies of acute cholangitis is how to set a gold standard for the disease against which to compare diagnostic and severity grading criteria. Unlike diseases such as acute cholecystitis there is no organ or tissue with which absolute diagnosis of acute cholangitis can be achieved pathologically. Therefore, a gold standard must be set by other means. An important step in generation of TG13 was to adopt the three gold standard diagnostic criteria suggested in the literature and by experience. This then permitted the gathering of a large number of example cases by which to refine and judge the adequacy of the new criteria. While this was an arduous task it seems that the results support this approach in dealing with these issues. Another novelty in our approach is that the diagnostic criteria were not judged simply against normal individuals but included patients with other biliary tract diseases especially acute cholecystitis. This increases the robustness of the criteria as a clinical tool.

The early iterations of the diagnostic criteria for TG13 included abdominal pain and a history of biliary tract disease; however, it was found that inclusion of these criteria resulted in a schema with low specificity and a high false positive rate in cases of acute cholecystitis. When these variables were dropped the results improved dramatically. It may seem odd to have diagnostic criteria which eliminate abdominal pain as a symptom of acute cholangitis but the benefit of eliminating confusion with other biliary tract disease if pain is included outweighs any advantage of including it.

The new TG13 diagnostic criteria have fewer variables and are arranged in more logical categories. The thresholds for laboratory tests have been selected to permit worldwide use as they do not depend on absolute values but on 1.5 times the upper limit of normal of any laboratory. As such these criteria should be amenable to use on handheld devices further improving the ability to rapidly diagnose the condition.

Ideally, a definitive diagnosis should be available at the time of presentation. If the requirement for a definitive diagnosis results in delay of biliary drainage with progression to more severe stages of the disease or death under observation the purpose of a definitive diagnosis is subverted. At the present state of knowledge our data suggest that the decision to proceed to early biliary drainage can and should be made on suspected diagnosis and severity grading as outlined in the paper as both of these can be determined at presentation. The effect of this strategy can be determined as the criteria for diagnosis are evaluated in the future.

The severity grading has also been revised based on new information available in the literature. The criteria for severe cases have not been modified but those in the important moderate group have been updated. As noted all

five criteria in the moderate group are determinable at presentation. This required the exclusion of a number of criteria as outlined in the results.

In practice the diagnostic criteria and severity grading would be used in tandem at the time of presentation. If a patient fit the suspected criteria, severity grading would be performed. Those falling into the moderate and severe categories would be candidates for urgent biliary decompression, while those in the mild category would be treated initially with antibiotics. Many of the latter patients would still have biliary drainage within the first 48 h for control of the cause of acute cholangitis such as extraction of common duct stones.

A diagnosis of acute cholangitis has traditionally been made by Charcot's triad. According to several reports, Charcot's triad was observed for only 9 % except in cases of acute cholangitis [8], but cases of acute cholangitis presenting all of Charcot's triad accounted for only 50–70 % [3, 8–14, 24–26]. We also continued to examine the utility of Charcot's triad because of the prominence of this diagnostic triad in this disease. We found that Charcot's triad shows very high specificity—the presence of the Charcot's triad strongly suggested the presence of acute cholangitis. However, due to the low sensitivity, it is not applicable in making a diagnosis of acute cholangitis. Also as noted the triad was not associated with disease severity.

In summary TG13 presents new diagnostic and severity grading systems based on a large patients base and a reasonable gold standard. These criteria allow early diagnosis and severity grading of the disease and should be clinically useful in the management of this severe disease.

Conclusion

TG13 introduces a new standard for the diagnosis, severity grading and management of acute cholangitis. As compared with Charcot's triad and TG07, validity of the diagnostic criteria has been improved and severity assessment criteria have become more suitable for clinical use.

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References

1. 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.
2. Dow R.W, Lindenauer SM. Acute obstructive suppurative cholangitis *Ann Surg* 1969; 169:272–6

3. Welch JP, Donaldson GA. The urgency of diagnosis and surgical treatment of acute suppurative cholangitis. *Am J Surg.* 1976;131: 527–32.
4. Blet JH, Way LW. Acute cholangitis. *Ann Surg* 1980;191: 264–70.
5. Saharia PC, Cameron JL. Clinical management of acute cholangitis. *Surg Gynec Obstet.* 1976;142:369–72.
6. Ostemiller W Jr, Thompson RJ Jr, Carter R, Hinshaw DB. Acute cholangitis. *World J Surg.* 1984;8:963–9.
7. 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.
8. Csendes A, Diaz JC, Burdiles P, Maluenda F, Morales E. Risk factors and classification of acute suppurative cholangitis. *Br J Surg.* 1992;79:655–8.
9. Thompson J, Bennion RS, Pitt HA. An analysis of infectious failures in acute cholangitis. *HPB Surg.* 1994;8:139–44.
10. Hui CK, Lai KC, Yuen MF, Ng M, Lai CL, Lam SK. Acute cholangitis—predictive factors for emergency ERCP. *Aliment Pharmacol Ther.* 2001;15:1633–7.
11. Gigot JF, Leese T, Dereme T, Coutinho J, Castaing D, Bismuth H. Acute cholangitis. Multivariate analysis of risk factors. *Ann Surg.* 1989;209:435–8.
12. Boey JH, Way LW. Acute cholangitis. *Ann Surg.* 1980;191: 264–70.
13. Lai EC, Tam PC, Paterson IA, Ng MM, Fan ST, Choi TK, et al. Emergency surgery for severe acute cholangitis. The high-risk patients. *Ann Surg.* 1990;211:55–9.
14. Lee CC, Chang IJ, Lai YC, Chen SY, Chen SC. Epidemiology and prognostic determinants of patients with bacteremic cholecystitis or cholangitis. *Am J Gastroenterol.* 2007;102:563–9.
15. Tai DI, Shen FH, Liaw YF. Abnormal pre-drainage serum creatinine as a prognostic indicator in acute cholangitis. *Hepato-gastroenterology.* 1992;39:47–50.
16. Andrew DJ, Johnson SE. Acute suppurative cholangitis, a medical and surgical emergency. A review of ten years experience emphasizing early recognition. *Am J Gastroenterol.* 1970;54: 141–54.
17. Rosing DK, De Virgilio C, Nguyen AT, El Masry M, Kaji AH, Stabile BE. Cholangitis: analysis of admission prognostic indicators and outcomes. *Am Surg* 2007;73:949–54
18. Hanau LH, Steigbigel NH. Acute (ascending) cholangitis. *Infect Dis Clin North Am.* 2000;14:521–46.
19. Tsujino T, Sugita R, Yoshida H, Yagioka H, Kogure H, Sasaki T, et al. Risk factors for acute suppurative cholangitis caused by bile duct stones. *Eur J Gastroenterol Hepatol.* 2007;19:585–8.
20. Shimada H, Nakagawara G, Kobayashi M, Tsuchiya S, Kudo T, Morita S. Pathogenesis and clinical features of acute cholangitis accompanied by shock. *Jpn J Surg.* 1984;14:269–77.
21. Yeom DH, Oh HJ, Son YW, Kim TH. What are the risk factors for acute suppurative cholangitis caused by common bile duct stones? *Gut Liver.* 2010;4:363–7. Epub 2010 Sep 24
22. Pang YY, Chun YA. Predictors for emergency biliary decompression in acute cholangitis. *Eur J Gastroenterol Hepatol.* 2006;18:727–31.
23. 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 Pancreatic Surg* 2007; 14:1–10.
24. Thompson JE Jr, Tompkins RK, Longmire WP Jr. Factors in management of acute cholangitis. *Ann Surg.* 1982;195:137–45.
25. O'Connor MJ, Schwartz ML, McQuarrie DG, Sumer HW. Acute bacterial cholangitis: an analysis of clinical manifestation. *Arch Surg.* 1982;117:437–41.
26. Hauptert AP, Carey LC, Evans WE, Ellison EH. Acute suppurative cholangitis. Experience with 15 consecutive cases. *Arch Surg.* 1967;94:460–8.