

Diagnostic criteria and severity assessment of acute cholecystitis: Tokyo Guidelines

MASAHIKO HIROTA¹, TADAHIRO TAKADA², YOSHIFUMI KAWARADA³, YUJI NIMURA⁴, FUMIHIKO MIURA², KOICHI HIRATA⁵, TOSHIHIKO MAYUMI⁶, MASAHIRO YOSHIDA², STEVEN STRASBERG⁷, HENRY PITT⁸, THOMAS R GADACZ⁹, EDUARDO DE SANTIBANES¹⁰, DIRK J. GOUMA¹¹, JOSEPH S. SOLOMKIN¹², JACQUES BELGHITI¹³, HORST NEUHAUS¹⁴, MARKUS W. BÜCHLER¹⁵, SHEUNG-TAT FAN¹⁶, CHEN-GUO KER¹⁷, ROBERT T. PADBURY¹⁸, KUI-HIN LIAU¹⁹, SERAFIN C. HILVANO²⁰, GIULIO BELLI²¹, JOHN A. WINDSOR²², and CHRISTOS DERVENIS²³

¹Department of Gastroenterological Surgery, Kumamoto University Graduate School of Medical Sciences, 1-1-1 Honjo, Kumamoto 860-8556, Japan

²Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan

³Mie University School of Medicine, Mie, Japan

⁴Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

⁵First Department of Surgery, Sapporo Medical University School of Medicine, Sapporo, Japan

⁶Department of Emergency Medicine and Critical Care, Nagoya University School of Medicine, Nagoya, Japan

⁷Department of Surgery, Indiana University School of Medicine, Indianapolis, USA

⁸Department of Surgery, Washington University in St Louis and Barnes-Jewish Hospital, St Louis, USA

⁹Department of Gastrointestinal Surgery, Medical College of Georgia, Georgia, USA

¹⁰Department of Surgery, University of Buenos Aires, Buenos Aires, Argentina

¹¹Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands

¹²Department of Surgery, Division of Trauma and Critical Care, University of Cincinnati College of Medicine, Cincinnati, USA

¹³Department of Digestive Surgery and Transplantation, Hospital Beaujon, Clichy, France

¹⁴Department of Internal Medicine, Evangelisches Krankenhaus Düsseldorf, Düsseldorf, Germany

¹⁵Department of Surgery, University of Heidelberg, Heidelberg, Germany

¹⁶Department of Surgery, The University of Hong Kong, Hong Kong, China

¹⁷Division of HBP Surgery, Yuan's General Hospital, Taoyuan, Taiwan

¹⁸Division of Surgical and Specialty Services, Flinders Medical Centre, Adelaide, Australia

¹⁹Department of Surgery, Tan Tock Seng Hospital / Hepatobiliary Surgery, Medical Centre, Singapore, Singapore

²⁰Department of Surgery, Philippine General Hospital, University of the Philippines, Manila, Philippines

²¹Department of General and HBP Surgery, Loreto Nuovo Hospital, Naples, Italy

²²Department of Surgery, The University of Auckland, Auckland, New Zealand

²³First Department of Surgery, Agia Olga Hospital, Athens, Greece

Abstract

The aim of this article is to propose new criteria for the diagnosis and severity assessment of acute cholecystitis, based on a systematic review of the literature and a consensus of experts. A working group reviewed articles with regard to the diagnosis and treatment of acute cholecystitis and extracted the best current available evidence. In addition to the evidence and face-to-face discussions, domestic consensus meetings were held by the experts in order to assess the results. A provisional outcome statement regarding the diagnostic criteria and criteria for severity assessment was discussed and finalized during an International Consensus Meeting held in Tokyo 2006. Patients exhibiting one of the local signs of inflammation, such as Murphy's sign, or a mass, pain or tenderness in the right upper quadrant, as well as one of the systemic signs of inflammation, such as fever, elevated white blood cell count, and elevated C-reactive protein level, are diagnosed as having acute cholecystitis. Patients in whom suspected clinical findings are confirmed by diagnostic imaging are also diagnosed with acute cholecystitis. The severity of acute cho-

lecystitis is classified into three grades, mild (grade I), moderate (grade II), and severe (grade III). Grade I (mild acute cholecystitis) is defined as acute cholecystitis in a patient with no organ dysfunction and limited disease in the gallbladder, making cholecystectomy a low-risk procedure. Grade II (moderate acute cholecystitis) is associated with no organ dysfunction but there is extensive disease in the gallbladder, resulting in difficulty in safely performing a cholecystectomy. Grade II disease is usually characterized by an elevated white blood cell count; a palpable, tender mass in the right upper abdominal quadrant; disease duration of more than 72 h; and imaging studies indicating significant inflammatory changes in the gallbladder. Grade III (severe acute cholecystitis) is defined as acute cholecystitis with organ dysfunction.

Key words Acute cholecystitis · Diagnosis · Severity of illness index · Guidelines · Infection

Introduction

Early diagnosis of acute cholecystitis allows prompt treatment and reduces both mortality and morbidity.

Offprint requests to: M. Hirota

Received: May 31, 2006 / Accepted: August 6, 2006

The accurate diagnosis of typical as well as atypical cases of acute cholecystitis requires specific diagnostic criteria. Acute cholecystitis has a better prognosis than acute cholangitis, but may require immediate management, especially in patients with torsion of the gallbladder and emphysematous, gangrenous, or suppurative cholecystitis. The lack of standard criteria for diagnosis and severity assessment is reflected by the wide range of reported mortality rates in the literature, and this lack makes it impossible to provide standardized optimal treatment guidelines for patients. In these Guidelines we propose specific criteria for the diagnosis and severity assessment of acute cholecystitis, based on the best available evidence and the experts' consensus achieved at the International Consensus Meeting for the Management of Acute Cholecystitis and Cholangitis, held on April 1–2, 2006, in Tokyo.

Diagnostic criteria for acute cholecystitis

Diagnosis is the starting point of the management of acute cholecystitis, and prompt and timely diagnosis should lead to early treatment and lower mortality and morbidity. Specific diagnostic criteria are necessary to accurately diagnose typical, as well as atypical cases. The Guidelines propose diagnostic criteria for acute cholecystitis (Table 1). C-reactive protein (CRP) is not

commonly measured in many countries. However, because acute cholecystitis is usually associated with an elevation of CRP level by 3 mg/dl or more, CRP was included. Diagnosis of acute cholecystitis by elevation of CRP level (3 mg/dl or more), with ultrasonographic findings suggesting acute cholecystitis, has a sensitivity of 97%, specificity of 76%, and positive predictive value of 95% (level 1b).¹ After the discussion during the Tokyo International Consensus Meeting, almost unanimous agreement was achieved on the criteria (Table 2). However, 19% of the panelists from abroad expressed the necessity for minor modifications, because, in the provisional version, the diagnostic criteria did not include technetium hepatobiliary iminodiacetic acid (Tc-HIDA) scan as an item.

Imaging findings of acute cholecystitis

Ultrasonography findings (level 4)²⁻⁵

Sonographic Murphy sign (tenderness elicited by pressing the gallbladder with the ultrasound probe)
Thickened gallbladder wall (>4mm; if the patient does not have chronic liver disease and/or ascites or right heart failure)
Enlarged gallbladder (long axis diameter >8cm, short axis diameter >4cm)
Incarcerated gallstone, debris echo, pericholecystic fluid collection
Sonolucent layer in the gallbladder wall, striated intramural lucencies, and Doppler signals.

Magnetic resonance imaging (MRI) findings (level 1b-4)⁶⁻⁹

Pericholecystic high signal
Enlarged gallbladder
Thickened gallbladder wall.

Computed tomography (CT) findings (level 3b)¹⁰

Thickened gallbladder wall
Pericholecystic fluid collection
Enlarged gallbladder
Linear high-density areas in the pericholecystic fat tissue.

Table 1. Diagnostic criteria for acute cholecystitis

A. Local signs of inflammation etc.:	(1) Murphy's sign, (2) RUQ mass/pain/tenderness
B. Systemic signs of inflammation etc.:	(1) Fever, (2) elevated CRP, (3) elevated WBC count
C. Imaging findings: imaging findings characteristic of acute cholecystitis	
Definite diagnosis	(1) One item in A and one item in B are positive (2) C confirms the diagnosis when acute cholecystitis is suspected clinically

Note: acute hepatitis, other acute abdominal diseases, and chronic cholecystitis should be excluded

Table 2. Answer pad responses on the diagnostic criteria for acute cholecystitis

	Agree	Agree, but needs minor modifications	Disagree
Total (<i>n</i> = 110)	92%	8%	0%
Panelists from abroad (<i>n</i> = 21)	81%	19%	0%
Japanese panelists (<i>n</i> = 20)	100%	0%	0%
Audience (<i>n</i> = 69)	93%	7%	0%

Tc-HIDA scans (level 4)^{11,12}

Non-visualized gallbladder with normal uptake and excretion of radioactivity
Rim sign (augmentation of radioactivity around the gallbladder fossa).

Severity assessment criteria of acute cholecystitis*Concept of severity grading of acute cholecystitis*

Patients with acute cholecystitis may present with a spectrum of disease stages ranging from a mild, self-limited illness to a fulminant, potentially life-threatening illness. In these Guidelines we classify the severity of acute cholecystitis into the following three categories: “mild (grade I)”, “moderate (grade II)”, and “severe (grade III)”. A category for the most severe grade of acute cholecystitis is needed because this grade requires intensive care and urgent treatment (operation and/or drainage) to save the patient’s life. However, the vast majority of patients present with less severe forms of the disease. In these patients, the major practical question regarding management is whether it is advisable to perform cholecystectomy at the time of presentation in the acute phase or whether other strategies of management should be chosen during the acute phase, followed by an interval cholecystectomy. Therefore, to guide the clinician, the severity grading includes a “moderate” group based on criteria predicting when conditions might be unfavorable for cholecystectomy in the acute phase (level 2b-4).^{13–18} Patients who fall neither into the severe nor the moderate group form the majority of patients with this disease; their disease is suitable for management by cholecystectomy in the acute phase, if comorbidities are not a factor. Definitions of the three grades are given below.

Mild (grade I) acute cholecystitis

Mild acute cholecystitis occurs in a patient in whom there are no findings of organ dysfunction, and there is mild disease in the gallbladder, allowing for cholecystectomy to be performed as a safe and low-risk procedure. These patients do not have a severity index that meets the criteria for “moderate (grade II)” or “severe (grade III)” acute cholecystitis.

Moderate (grade II) acute cholecystitis

In moderate acute cholecystitis, the degree of acute inflammation is likely to be associated with increased operative difficulty to perform a cholecystectomy (level 2b-4).^{13–18}

Severe (grade III) acute cholecystitis

Severe acute cholecystitis is associated with organ dysfunction.

Criteria for the severity assessment of acute cholecystitis

Acute cholecystitis has a better outcome/prognosis than acute cholangitis but requires prompt treatment if gangrenous cholecystitis, emphysematous cholecystitis, or torsion of the gallbladder are present. The progression of acute cholecystitis from the mild/moderate to the severe form means the development of the multiple organ dysfunction syndrome (MODS). Organ dysfunction scores, such as Marshall’s multiple organ dysfunction (MOD) score, and the sequential organ failure assessment (SOFA) score, are sometimes used to evaluate organ dysfunction in critically ill patients. The Guidelines classify the severity of acute cholecystitis into three grades (Tables 3–5): “severe (grade III)”: acute cholecystitis associated with organ dysfunction, “moderate (grade II)”: acute cholecystitis associated with difficulty to perform cholecystectomy due to local inflammation, and “mild (grade I)”: acute cholecystitis which does not meet the criteria of “severe” or “moderate” acute cholecystitis (these patients have acute cholecystitis but no

Table 3. Criteria for mild (grade I) acute cholecystitis

“Mild (grade I)” acute cholecystitis does not meet the criteria of “severe (grade III)” or “moderate (grade II)” acute cholecystitis. Grade I can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and only mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.

Table 4. Criteria for moderate (grade II) acute cholecystitis

“Moderate” acute cholecystitis is accompanied by any one of the following conditions:

1. Elevated WBC count ($>18000/\text{mm}^3$)
2. Palpable tender mass in the right upper abdominal quadrant
3. Duration of complaints $>72\text{h}^a$
4. Marked local inflammation (biliary peritonitis, pericholecystic abscess, hepatic abscess, gangrenous cholecystitis, emphysematous cholecystitis)

^aLaparoscopic surgery in acute cholecystitis should be performed within 96h after the onset (level 2b-4)^{13,14,16}

Table 5. Criteria for severe (grade III) acute cholecystitis

“Severe” acute cholecystitis is accompanied by dysfunctions in any one of the following organs/systems

1. Cardiovascular dysfunction (hypotension requiring treatment with dopamine $\geq 5\mu\text{g}/\text{kg}$ per min, or any dose of dobutamine)
2. Neurological dysfunction (decreased level of consciousness)
3. Respiratory dysfunction ($\text{PaO}_2/\text{FiO}_2$ ratio <300)
4. Renal dysfunction (oliguria, creatinine $>2.0\text{mg}/\text{dl}$)
5. Hepatic dysfunction (PT-INR >1.5)
6. Hematological dysfunction (platelet count $<100000/\text{mm}^3$)

Table 6. Answer pad responses on the criteria for severe (grade III) acute cholecystitis

	Agree	Agree, but needs minor modifications	Disagree
Total ($n = 110$)	90%	10%	0%
Panelists from abroad ($n = 21$)	95%	5%	0%
Japanese panelists ($n = 21$)	81%	19%	0%
Audience ($n = 68$)	91%	9%	0%

Table 7. Answer pad responses on the criteria for moderate (grade II) acute cholecystitis

	Agree	Agree, but needs minor modifications	Disagree
Total ($n = 109$)	78%	22%	0%
Panelists from abroad ($n = 22$)	77%	23%	0%
Japanese panelists ($n = 22$)	91%	9%	0%
Audience ($n = 65$)	74%	26%	0%

organ dysfunction, and there are mild inflammatory changes in the gallbladder, so that a cholecystectomy can be performed with a low operative risk). Almost unanimous agreement on the criteria was achieved (Tables 6 and 7). When acute cholecystitis is accompanied by acute cholangitis, the criteria for the severity assessment of acute cholangitis should also be taken into account. Being “elderly” per se is not a criterion for severity itself, but indicates a propensity to progress to the severe form, and thus is not included in the criteria for severity assessment.

Acknowledgments. We would like to express our deep gratitude to the Japanese Society for Abdominal Emergency Medicine, the Japan Biliary Association, and the Japanese Society of Hepato-Biliary-Pancreatic Surgery, who provided us with great support and guidance in the preparation of the Guidelines. This process was conducted as part of the Project on the Preparation and Diffusion of Guidelines for the Management of Acute Cholangitis (H-15-Medicine-30), with a research subsidy for fiscal 2003 and 2004 (Integrated Research Project for Assessing Medical Technology), sponsored by the Japanese Ministry of Health, Labour, and Welfare.

We also truly appreciate the panelists who cooperated with and contributed significantly to the International Consensus Meeting held on April 1 and 2, 2006.

References

- Juvonen T, Kiviniemi H, Niemela O, Kairaluoma MI. Diagnostic accuracy of ultrasonography and C-reactive protein concentration in acute cholecystitis: a prospective clinical study. *Eur J Surg* 1992;158:365–9 (level 1b).
- Ralls PW, Colletti PM, Lapin SA, Chandrasoma P, Boswell WD Jr, Ngo C, et al. Real-time sonography in suspected acute cholecystitis. Prospective evaluation of primary and secondary signs. *Radiology* 1985;155:767–71 (level 4).
- Martinez A, Bona X, Velasco M, Martin J. Diagnostic accuracy of ultrasound in acute cholecystitis. *Gastrointest Radiol* 1986;11:334–8 (level 4).
- Ralls PW, Halls J, Lapin SA, Quinn MF, Morris UL, Boswell W. Prospective evaluation of the sonographic Murphy sign in suspected acute cholecystitis. *J Clin Ultrasound* 1982;10:113–5 (level 4).
- Bree RL. Further observations on the usefulness of the sonographic Murphy sign in the evaluation of suspected acute cholecystitis. *J Clin Ultrasound* 1995;23:169–72 (level 4).
- Hakansson K, Leander P, Ekberg O, Hakansson HO. MR imaging in clinically suspected acute cholecystitis. A comparison with ultrasonography. *Acta Radiol* 2000;41:322–8 (level 2b).
- Regan F, Schaefer DC, Smith DP, Petronis JD, Bohlman ME, Magnuson TH. The diagnostic utility of HASTE MRI in the evaluation of acute cholecystitis: half-Fourier acquisition single-shot turbo SE. *J Comput Assist Tomogr* 1998;22:638–42 (level 4).
- Shea JA, Berlin JA, Escarce JJ, Clarke JR, Kinoshian BP, Cabana MD, et al. Revised estimates of diagnostic test sensitivity and specificity in suspected biliary tract disease. *Arch Intern Med* 1994;154:2573–81 (level 1b).
- Ito K, Fujita N, Noda Y, Kobayashi G, Kimura K, Katakura Y, et al. The significance of magnetic resonance cholangiopancreatography in acute cholecystitis (in Japanese with English abstract). *Jpn J Gastroenterol* 2000;97:1472–9 (level 4).

10. Fidler J, Paulson EK, Layfield L. CT evaluation of acute cholecystitis: findings and usefulness in diagnosis. *Am J Roentgenol* 1996;166:1085–8 (level 3b).
11. Mauro MA, McCartney WH, Melmed JR. Hepatobiliary scanning with 99m Tc-PIPIDA in acute cholecystitis. *Radiology* 1982;142:193–7 (level 4).
12. Bushnell DL, Perlman SB, Wilson MA, Polcyn RE. The rim sign: association with acute cholecystitis. *J Nucl Med* 1986;27:353–6 (level 4).
13. Brodsky A, Matter I, Sabo E, Cohen A, Abrahamson J, Eldar S. Laparoscopic cholecystectomy for acute cholecystitis: can the need for conversion and the probability of complications be predicted? A prospective study. *Surg Endosc* 2000;14:755–60 (level 2b).
14. Teixeira JP, Sraiva AC, Cabral AC, Barros H, Reis JR, Teixeira A. Conversion factors in laparoscopic cholecystectomy for acute cholecystitis. *Hepatogastroenterology* 2000;47:626–30 (level 2b).
15. Halachmi S, DiCastro N, Matter I, Cohen A, Sabo E, Mogilner JG, et al. Laparoscopic cholecystectomy for acute cholecystitis: how do fever and leucocytosis relate to conversion and complications? *Eur J Surg* 2000;166:136–40 (level 2b).
16. Araujo-Teixeria JP, Rocha-Reis J, Costa-Cabral A, Barros H, Saraiva AC, Araujo-Teixeira AM. Laparoscopic versus open cholecystectomy for cholecystitis (200 cases). Comparison of results and predictive factors for conversion (in French with English abstract). *Chirurgie* 1999;124:529–35 (level 4).
17. Rattner DW, Ferguson C, Warshaw AL. Factors associated with successful laparoscopic cholecystectomy for acute cholecystitis. *Ann Surg* 1993;217:233–6 (level 2b).
18. Merriam LT, Kanaan SA, Dawes JG, Angelos P, Prystowsky JB, Rege RV, et al. Gangrenous cholecystitis: analysis of risk factors and experience with laparoscopic cholecystectomy. *Surgery* 1999;126:680–5 (level 4).

Discussion at the Tokyo International Consensus Meeting

Diagnostic criteria for acute cholecystitis

The clinical diagnosis of acute cholecystitis is traditionally based on the patient's clinical presentation, and it is confirmed by the imaging findings. Hence, the initial provisional diagnostic criteria for acute cholecystitis comprised: (1) clinical signs and symptoms, (2) laboratory data, and (3) imaging findings. In the discussion on criteria for "clinical signs and symptoms", 92% of the Japanese panelists agreed, whereas only 65% of the panelists from abroad agreed and 4% disagreed. In regard to the criteria for "laboratory data", 20% of the

Japanese panelists and 39% of the panelists from abroad voted "agree, but needs minor modifications". After a discussion among the panelists, several changes were made. In regard to the proposed criteria for "imaging findings", 66%–71% of the Japanese panelists agreed and about 30% of the panelists voted "agree, but needs minor modifications", and 4% of the panelists from abroad disagreed, because Tc-HIDA scans were not included. Discussion at the International Consensus Meeting led to the reorganization of these categories as: (1) local signs of inflammation, (2) systemic signs of inflammation, and (3) imaging findings. "Suspected diagnosis" in the provisional criteria was deleted, and two conditions for "definite diagnosis" were established in the final diagnostic criteria. After the discussion, 100% of the Japanese panelists and 81% of the panelists from abroad agreed on the final version (refer to Tables 1 and 2; consensus was reached).

Severity assessment criteria for acute cholecystitis

Concerning criteria for severe (grade III) acute cholecystitis, 81% of the Japanese panelists and 95% of the panelists from abroad agreed with the criteria (refer to Tables 5 and 6; consensus was reached). The acute physiology and chronic health evaluation II (APACHE II) score was not included in the assessment criteria, because it is too complicated to apply in community hospitals.

The criteria for moderate (grade II) acute cholecystitis can be defined as acute cholecystitis associated with local inflammatory conditions that make cholecystectomy difficult (Steven Strasberg, USA; Dirk J. Gouma, the Netherlands; Henry Pitt, USA; Sheung-Tat Fan and Joseph W.Y. Lau, Hong Kong; Serafin C. Hilvano, Philippines). On the basis of these aspects, the final criteria for moderate (grade II) acute cholecystitis were defined and were agreed on by 91% of the Japanese panelists and 77% of those from abroad (refer to Tables 4 and 7; consensus was reached).

The criteria for mild (grade I) acute cholecystitis were agreed on by approximately 90% of both the Japanese panelists and the panelists from abroad (consensus was reached).