Manuscript 4

Flowchart for Diagnosis and Treatment of Acute Cholangitis and Cholecystitis – Tokyo Guidelines

Running title: Mangement strategy for biliary infection

Abstract

Diagnostic and therapeutic strategy for acute biliary infection (acute cholangitis and acute cholecystitis) according to the severity has not been established in the world. Thus, we formulated the flowcharts for the management of acute biliary infection in accordance with severity.

For severe acute cholangitis appropriate organ support such as ventilation/circulation management are required. After stabilizing hemodynamic state urgent endoscopic or percutaneous transhepatic biliary drainage (emergent surgery such as choledochotomy with T-tube insertion if neither procedure is possible) should be performed. For moederate acute cholangitis early biliary drainage should be performed. For patients with choledocolithiasis, immediate endoscopic sphincterotomy and stone extraction or one-stage surgery may be indicated when general condition is stable. For mild acute cholangitis medical treatment may be enough. However, the cases with choledocholithiasis or no response to the medical treatment should be subjected to biliary drainage or one-stage surgery.

For patients with severe acute cholecystitis urgent/ early cholecystectomy with adequate management of systemic conditions should be indicated. If patients have surgical risk, urgent percutaneous gallbladder drainage may be performed. Cholecystectomy can be done after patients' condition improves. For patients with moderate acute cholecystitis urgent/ early cholecystectomy should be performed. If patients have surgical risk, temporally GB drainage should be selected. For patients with mild cholecystitis medical treatment should be continued. It is desirable to apply cholecystectomy after disappearance of inflammation for preventing recurrence.

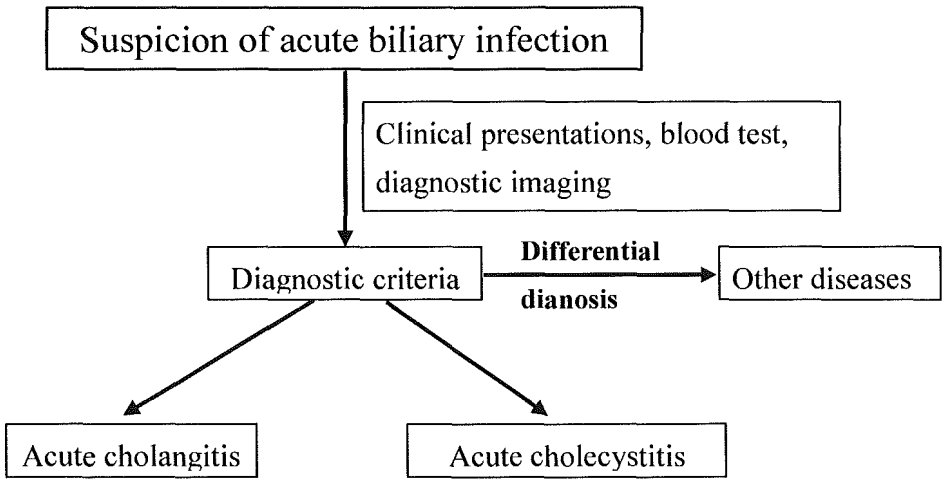
Key words: Acute cholangitis, Acute cholecystitis, Cholecystectomy, Laparoscopic cholecystectomy, Biliary drainage

INTRODUCTION

Acute biliary infection is divided into acute cholangitis and acute cholecystitis, and ranges from mild cases that can be mitigated only by medical treatment to severe cases requiring intensive care and urgent intervention. Conditions of patients with biliary infection are likely to deteriorate rapidly and to be life-threatening. Early diagnosis should be made based on clinical signs and examination findings, and suitable treatment according to the severity should be given at the right time.

Although endoscopic and laparoscopic techniques have improved recently (level 1b-2b)[1,2], results of treatment for severe acute biliary infection is still fatal. To our knowledge there is no definite diagnostic and therapeutic guidelines for acute biliary infection according to the severity. This article describes the management strategy for biliary infection in accordance with severity which was established through earnest discussion in the International Consensus Meeting on April 1-2 of 2006 in Tokyo.

Figure 1. Flowchart for the management of acute biliary infection



Flowchart of the initial approach to acute biliary infection (Figure 1)

Clinical presentations

Clinical signs, which acute cholangitis is strongly suspected, are fever, abdominal pain and jaundice (Charcot's triad). The triad was reported as the symptoms of hepatic fever by Charcot in 1887[3] and has been historically used as the useful clinical findings of acute cholangitis. However, only about 50 – 70% of the patients satisfied all three symptoms (Level 2b-4) [4-7]. The Reynolds' pentad, Charcot's triad plus shock and disturbance of consciousness, were presented in 1959, when Reynolds and Dargan[8] defined acute obstructive cholangitis. The pentad is often used as symptoms representing severe cholangitis, but shock and disturbed consciousness are observed only in 30% or less cases with acute cholangitis (Level 2b-4)[4-7]. History of colic pain, previous biliary surgery and biliary stent placement are informative.

Clinical symptoms of acute cholecystitis include abdominal pain (right upper abdominal pain), nausea, vomiting and fever (Level 2b-4)[9-11]. The most typical symptom is right hypochondriac pain. Tenderness at the right upper abdomen, palpable gallbladder, and Murphy's sign are the characteristic findings of acute cholecystitis. Murphy's sign specific to acute cholecystitis has high specificity of 79 – 96% (level 2b-3b) [9, 11].

Blood test

Diagnosis of acute cholangitis requires the measurement of white blood cell count, C-reactive protein, alkaline phosphatase, γ-Glutamyltranspeptidase, and bilirubin. For severity assessment platelet count, blood urea nitrogen, creatinine, and albumin should be measured. Blood culture is helpful for severity assessment as well as selection of antimicrobial drugs. Hyperamylasemia is a useful parameter to identify complications such as choledocholithiasis associated biliary pancreatitis (Level Ia)[12].

Regarding acute cholecystitis there is no specific blood test to confirm the diagnosis. However the measurement of white blood cell count and C-reacrtive protein is indispensable for diagnosis. For severity assessment bilirubin, blood urea nitrogen, and creatinine should be measured.

Diagnostic imaging

In the diagnostic imaging, abdominal ultrasonic examination should be applied first to all cases suspected of acute biliary infection. Ultrasonic examination has satisfactory diagnostic capability even when it is performed not only by specialists of ultrasound but also by emergency physicians (Level 1b) [13, 14].

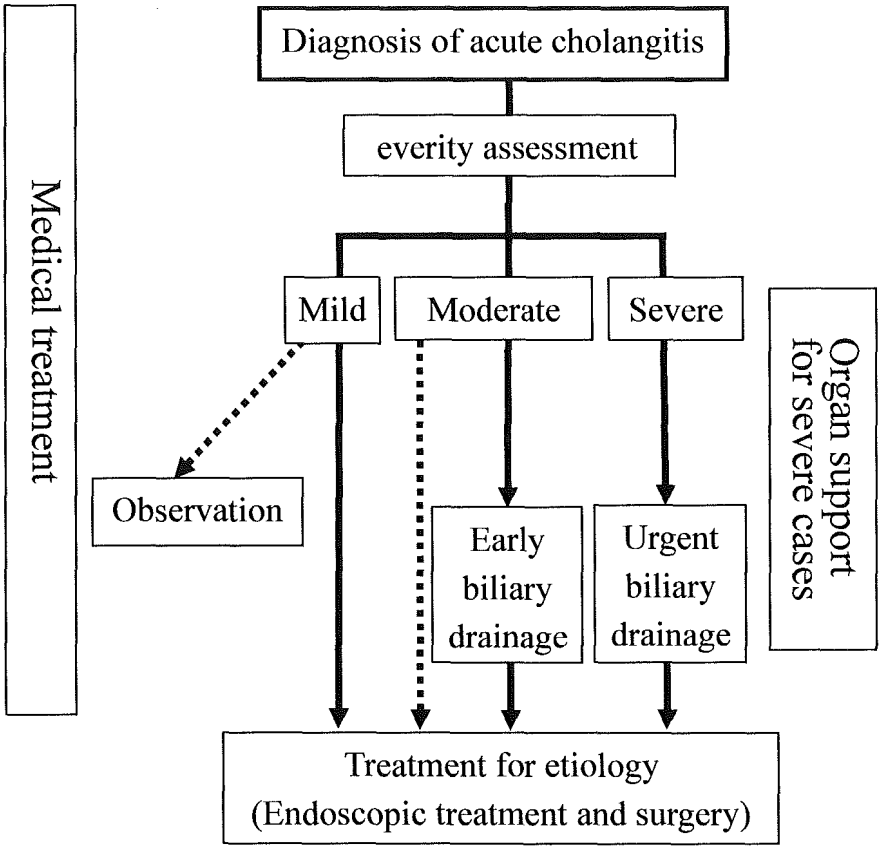
The role of the diagnostic imaging in acute cholangitis is to determine the presence/absence of biliary obstruction, the level of obstruction and its causes, such as gallstone and biliary stricture. The assessment could be performed by Ultrasonic examination and CT scanning. Both may obtain indirect findings, such as dilatation of bile duct and pneumobilia.

Acute cholecystitis shows finding such as enlarged gallbladder, thickened gallbladder wall, gallbladder stone and debris echo in the gallbladder internal debris, sonographic Murphy's signs, pericholecystic fluid collection and pericholecystic abscess. Sonographic Murphy's signs are most reliable findings of acute cholecystitis with specificity exceeding 90% (Level 3b,4) [15, 16]. It is also necessary to confirm the presence/absence of pneumobilia, ileus image and free air by using plain x-ray.

Differential diagnosis

Diseases which should be differentiated from acute cholangitis are acute cholecystitis, gastric and duodenal ulcer, acute pancreatitis and acute hepatitis. Diseases which should be differentiated from acute cholecystitis are gastric and duodenal ulcer, gallbladder cancer, hepatic abscess, Fitz-Hugh-Curtis syndrome, right lower lobar pheumonia, angina pectoris and myocardial infarction.

Figure2. Flowchart for the management of acute cholangitis



Flowchart for the management of acute cholangitis (Figure 2)

Treatment of acute cholangitis should be decided according to the severity. Many of patients with acute cholangitis cannot be saved by the conservative treatment alone (level 4)[6, 7]. Biliary drainage plays the most important role in the treatment of acute cholangitis. When diagnosis of acute cholangitis is suspected medical treatment including N.P.O., intravenous fluids, antibiotics, and analgesia, together with close monitoring of blood pressure, pulse and urinary output should be launched. Simultaneously severity assessment should be made. Appropriate treatment should be performed in accordance with severity. Patients with concomitant disease, acute pancreatitis or malignant disease and elderly are likely to progress to severe cases, therefore such patients should be managed carefully.

Severe acute cholangitis

Appropriate organ support such as ventilation/circulation management (endotracheal intubation, artificial respiration management, use of vasopressor, etc.) and treatment for disseminatated intravascular coagulopathy (DIC) are required, if necessary, in addition to medical treatment. After stabilizing hemodynamic state urgent endoscopic or percutaneous transhepatic biliary drainage (where neither procedure is possible an emergent operation of the decompression of the bile duct with a T-tube) should be performed. These procedures should be limited to decompression of the biliary system. Treatment for etilology such as bile duct stones should be taken into consideration when acute illness has resolved.

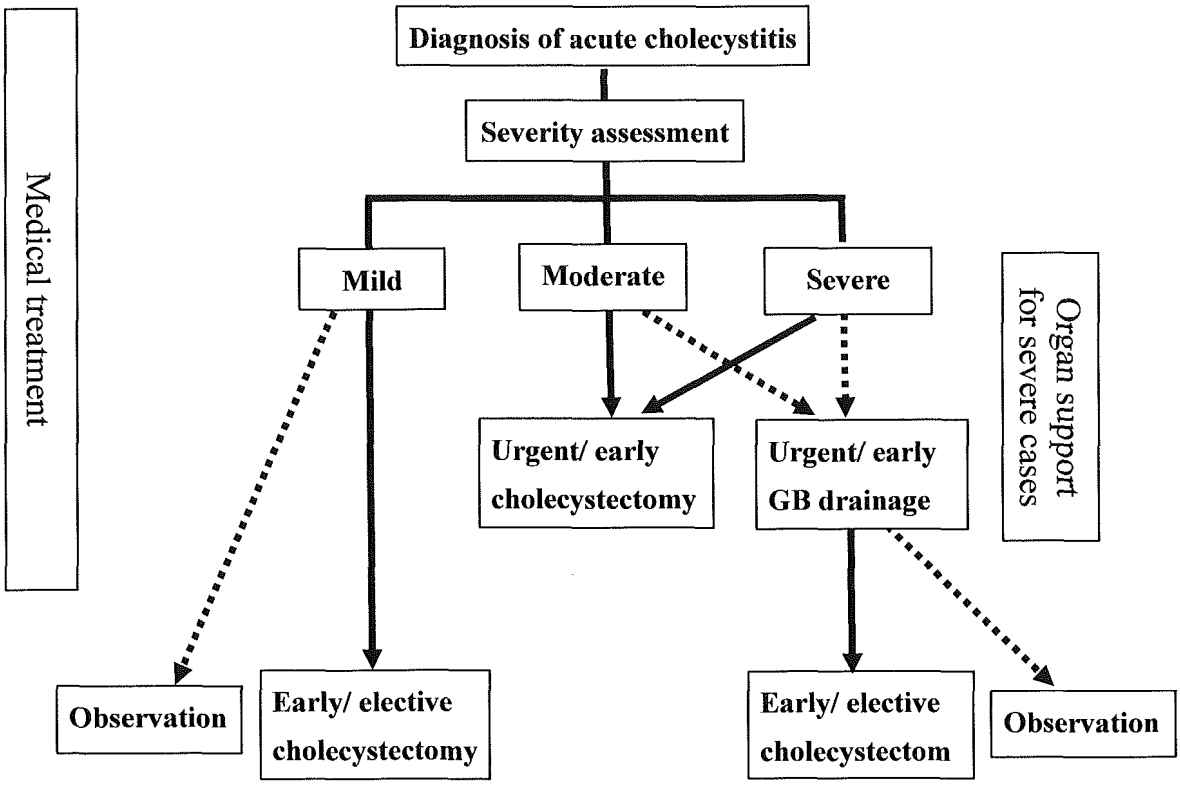
Moderate acute cholangitis

Early endoscopic or percutaneous transhepatic biliary drainage or surgical decompression should be performed. For patients with choledocolithiasis, immediate endoscopic sphincterotomy and stone extraction or one step surgery may be indicated when general condition is stable.

Mild acute cholangitis

Medical treatment following primary care should be continued. Biliary drainage is not required in most cases.

Figure 3. Flowchart for the management of acute cholecystitis



GB; gallbladder

Flowchart for the management of acute cholecystitis (Figure 3)

Basic treatment is early/urgent cholecystectomy for acute cholecystitis. Percutaneous gallbladder (GB) drainage is an alternative therapy for patients who cannot undergo urgent/ early cholecystectomy due to surgical risk (level 4)[17, 18].

When diagnosis of acute cholecystitis is suspected medical treatment including N.P.O., intravenous fluids, antibiotics, and analgesia, together with close monitoring of blood pressure, pulse and urinary output should be launched. Simultaneously severity assessment should be made. Appropriate treatment should be performed in accordance with severity. Elderly patients are likely to progress to severe. Acalculous cholecystitis sometimes does not respond to medical treatment and is often complicated by gangrene (level 4)[19, 20].

Severe acute cholecystitis

Urgent/ early cholecystectomy with adequate management of systemic conditions should be indicated. If patients have surgical risk, urgent/ early GB drainage may be performed. After patients' condition improves by gallbladder drainage cholecystectomy can be done. In surgically high-risk patients and patients with acalculous cholecystitis, observation may be selected.

Moderate acute cholecystitis

Urgent/ early cholecystectomy should be performed. If patients have surgical risk, temporally GB drainage should be selected. After patients' condition improves by GB drainage cholecystectomy can be done. In surgically high-risk patients and patients with acalculous cholecystitis, observation may be considered.

Mild acute cholecystitis

Medical treatment should be continued. It is desirable to apply cholecystectomy for preventing recurrence.

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Manuscript 5

Diagnostic Criteria and Severity Assessment of Acute Cholangitis: Tokyo Guidelines

Running title: Diagnosis of acute cholangitis

Abstract

Acute cholangitis has a potential to rapidly progress to a severe form which is accompanied with shock and/or organ failure(s), so that prompt diagnosis as well as severity assessment is necessary for appropriate management which includes urgent biliary drainage. However, there were no standard criteria of diagnosis and severity assessment of acute cholangitis then no practical guideline has been established for the management of this disease. The aim of this article is to propose new diagnostic criteria and severity assessment of acute cholangitis as a result of systematic review of literatures and expert consensus opinions.

A working group reviewed articles with regard to the diagnosis and treatment of acute cholangitis and extracted the best current available evidence in this area. In addition to the evidence face-to-face discussions, domestic consensus meetings were held by the experts in order to assess the outcome. Final outcome statement regarding the diagnostic criteria and severity assessment was clarified through the International Consensus Meeting in Tokyo 2006.

Key words: Acute cholangitis, Diagnostic criteria, Severity assessment

Introduction

The pathophysiology of acute cholangitis is biliary infection in association with partial or complete obstruction of the biliary system which is caused by various etiologies, including choledocholithiasis, benign and malignant strictures, biliary enteteric anastomotic strictures, and indwelling biliary stent malfunction. The clinical triad of fever, abdominal pain and jaundice associated with cholangitis was first described by Charcot in 1877 [1]. Charcot's triad is frequently used for the diagnosis of acute cholangitis in clinical practice but the triad can be seen in only 50-70% of all patients having acute cholnagitis, i.e. it is impossible to diagnose 30-50% of all patients as having acute cholangitis by Charcot's triad [3-10]. Various definitions have been used in literatures and no standard diagnostic criteria are established yet [3-10].

In addition to the diagnosis, the severity assessment is also important because clinical presentation of acute cholangitis varies in severity from mild and self-limited illness to severe and potentially life-threatening illness, and the latter is required urgent biliary drainage for saving life. In 1959, Reynolds and Dargan reported the cases presenting lethargy or mental confusions and shock together with Charcot's triad (Reynold's pentad) caused by biliary obstruction, and concluded that emergent surgical biliary decompression is an only effective procedure for treating the disease [2]. Reynolds' pentad have been used as important clinical signs of severe cholangitis but it is extremely rare that all components of pentad are observed even in severe acute cholangitis, approximately less than 10% [Ref]. No standard criteria for severity assessment of acute cholangitis are established yet.

The lack of standard criteria of diagnosis and severity assessment is reflected by the wide range of reported mortality rate in literatures [Ref], and makes it impossible to provide homogeneous best treatment for the patients with this disease. In this manuscript we propose new diagnostic criteria and severity assessment of acute cholangitis based on the best available evidence and expert's consensus which is achieved through the International Consensus Meeting for the Management of Acute Cholecystitis, Cholangitis held in April 1-2, 2006 in Tokyo.

Diagnostic criteria

A variety of names and definitions representing acute cholangitis were found in the literatures depending on authors [ref] (Table 1). Some authors define acute cholangitis based on clinical sign's such as Charcot's triad (fever, abdominal pain and jaundice), while others put emphasis on the presence or absence of biliary obstruction and the property of bile (suppurative or non-suppurative cholangitis). Thus no standard diagnostic criteria for acute cholangitis are presented yet.

Clinical signs have been used as important factors in the diagnosis of acute cholangitis. Table 2 summarized the incidence of each clinical sign in literatures of acute cholangitis. Fever and abdominal pain are the most frequently observed clinical signs with the incidence of up to 80% or more of acute cholangitis cases, whereas jaundice is observed in 60-70% of the cases (level 2b-4)[3,4,6,8-10,18,19]. The cases presenting all components of Charcot's triad account for 15.4-72% of all acute cholangitis cases[3-10], while triad is observed only in 3% of other cases than cholangitis cases (level 2b) [3]. Thus, the specificity of Charcot's triad for diagnostic use is relatively high for patients with acute cholangitis but the sensitivity is quite low. As Charcot's triad fails to diagnose about one third of patients having acute cholangitis, we propose new criteria for the diagnosis of acute cholangitis (Table 3). Basic concepts of the criteria are as follows: (1) Charcot's triad is the definite criteria for diagnosis of acute cholangitis, (2) If a patient does not have all component of Charcot's triad then definite diagnosis can be achieved if both "biliary infection" and "biliary obstruction (or cholestasis)" are proven by blood test and imaging findings. Positive rate of each blood test in literatures are listed in Table 4.

Severity assessment

Definition of severe acute cholangitis

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

(1) Severe acute cholangitis
Cholangitis, which presents systemic symptoms due to sepsis, and may become fatal unless urgent biliary drainage and organ support are applied.
(2) Moderate acute cholangitis
Cholangitis, which has no organ dysfunction, but is likely to have it and should undergo biliary drainage.
(3) Mild acute cholangitis
Cholangitis, which can undergo conservative treatment and delayed etiology identification and treatment (endoscopic treatment and surgery)

Severity assessment criteria

The progression of acute cholangitis into severe form means the occurrence of Multi-Organ Dysfunction Syndrome (MODS), such as acute renal failure and syndrome of disseminated intravascular coagulation (DIC), from sepsis due to increased intraductal pressure with reflux of infected bile into the sinusoid and blood vessels. Severe acute cholangitis was characterized by the following three common features in the literatures, (1) no response to conservative treatment, (2) presence of complications of organ failure and (3) necessity of prompt biliary drainage [Ref].

Organ failure scores, such as Marshall's MOF score, SOFA score, are sometimes used to evaluate organ failures in critically ill patients. But in this severity assessment of acute cholangitis, using these score is cumbersome, and moreover there is not enough evidence that each cut off point is meaning value in assessment of severity of the disease. Moreover in both scores serum bilirubin is used as an index of liver failure, however hyperbilirubinemia may be always present in acute cholangitis causing overestimation of these system.
Therefore, at this point, we formulated a simple severity assessment criteria in considering MODS scores. In future, severity scores based on these organ failure scores may show significant value in evaluation of the patients in severity of acute cholangitis.

Several risk factors in favor of poor prognosis for the patients with acute cholangitis have been reported in the literatures, and are summarized in Table 5 [Ref]. In formulating the criteria for the severity assessment of acute cholangitis, we emphasized on the necessity and timing of biliary drainage as well as organ support. (Table 6).

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Table 1. Names and definition of diseases used in references for acute cholangitis

Author	Disease	Diagnostic criteria		
		Clinical signs	Biliary obstruction	Bile property
Csendes[3]	ASC			Turbid or frank pus (Aspirated CBD fluid)
Thompson[4]	AC	Clinical evidence of infection and biliary obstruction confirmed by radiologic, operative, or postmortem findings biliary tube in place in whom obstruction to free flow of bile or other tube malfunction		
Gigot[5]	AC	A clinical picture of cholestasis and infection with positive blood and/or bile culture	An anomaly -usually an obstruction- of the biliary tract	
Boey[6]	AC	Clinical evidence of infection (fever, chills, leucocytosis, abdominal pain or tenderness) of biliary tract obstruction (jaundice, elevated Bile and alkaline phosphatase)	Evidence of biliary tract obstruction confirmed by radiological or operative findings	
	SC		Total or nearly occlusion	With pus
	NonSC			Without pus
O'Connor[7]	AC	Symptom biliary fever and chills, jaundice, or abdominal pain	Mechanical obstruction of the biliary tree (roentgenographic, operative, or postmortem)	
	SC NonSC			Purulence No purulence
Lai[8]	Severe AC	The presence of hyperbilirubinemia with either fever or abdominal pain, progression of biliary sepsis		
Haupert[9]	ASC	(Acute illness)	Evidence of obstruction of CBD	Frank pus in CBD
Welch[10]	ASC	Abdominal pain; fever; chills, and leucocytosis; jaundice		Purulence at surgery or autopsy
	AOSC	Added CNS confusion; bacteremia with hypotension	Complete biliary obstruction	CBD pus under pressure, possible liver abscesses
Saharia[18]	AC	Clinical symptoms	Biopsy of the liver or operation, or both, or autopsy findings	
Chijiiwa[19]	AOSC	Abdominal pain, jaundice, fever	Evidence of complete duct obstruction	Purulent bile

AC: acute cholangitis, SC: suppurative cholangitis, AOSC: acute obstructive suppurative cholangitis