Review Article

Endoscopic management of acute cholangitis

Background

Acute cholangitis is a systemic infectious condition with acute inflammation and infection in the bile duct. The incidence of acute cholangitis ranges from 0.3 to 1.6% with a proportion of severe cholangitis that reaches 12.3%. A proportion of acute cholangitis occurs after ERCP in about 0.5-2.4%. The most common cause of acute cholangitis is common bile duct stone.

Mortality rate in severe cholangitis remains significant without appropriate management. Advances in intensive care, antibiotic regimens and biliary drainage techniques have dramatically improved the mortality rate of more than 50% prior to the 1970s to less than 10% in the 1980s. Anyway still it remains about 3-10%. Clinical presentation ranges from mild symptoms to severe life-threatening with septic shock conducting rapidly to death.

Diagnosis is not more based on Charcot triad or Reynold pentad because of low sensitivity. The diagnostic criteria according to the Tokio guideline is mainly based on presence of systemic inflammation, cholestasis and or jaundice and evidence on imaging studies of biliary obstruction.

Classification of severity is determined by the Tokio criteria that distinguish severe cholangitis that is associated with the onset of organ dysfunction from moderate that is associated with the onset of clinical signs and symptoms. Mild cholangitis does not meet the diagnostic criteria of severe or moderate cholangitis at initial diagnosis.

The rationale of the treatment is based on pathophysiology and taking into account the increased presence of bacteria inthe bile duct (bactibilia), biliary obstruction and aetiology. Therefore,antibiotic treatment started as soon as possible and biliary drainage are the treatment of choice.

Epidemiology

No large epidemiological study has been conducted to date, but it can be estimated that approximately 10 % of the general population have gallstone.[1] According to a review by Friedman, 1-2 % of patients with asymptomatic gallstones and 1-3 % of patients with mild symptoms annually presented severe symptoms or complications (acute cholecystitis, acute cholangitis, severe jaundice, or pancreatitis).[1] The probability of undergoing operation due to subsequent severe symptoms was 6-8 %/year in patients initially presenting moderate symptoms and the symptoms decreased year by year.[1]

The data coming from observational studies show that 20-40 % of patients with asymptomatic cholelithiasis have a risk for developing some type of symptoms and/or signs (1-3 % annually.[1–6] The proportion of cases diagnosed as severe (grade III) according to the TG07 severity assessment criteria was12.3 %.[7] It has been reported that the mortality rate of acute cholangitis was higher than 50 % before 1980, 10-30 % in1981-1990s, and 2.7-10 % after 2000 (8,9).The mortality rate in patients with acute cholangitis ranges from 2.7% to10%. Following endoscopic sphincterectomy (EST), recurrence occurred in 7-47 % of cases with complications in the biliary tract system (cholelithiasis, biliary tract colic, cholangitis) within the 2.5-15year follow-up period.[10–15] The recurrence rates of bile duct stones are

Alberto Tringali
Endoscopic Unit, Niguarda Hospital, Italy

Correspondence: Alberto Tringali, Endoscopic Unit, Niguarda Hospital, Milan (Italy),Tel 3.90264442901, Fax 3.90264E+11, Email lringali@ospedaleniguarda.it

the same in the ES and EPBD (5.5 and8.8 % respectively) for both treatment methods.[16]

Etiology

The etiology of acute cholangitis are summarized in Table 1. Choledocholithiasis used to be the most frequent cause, but recently the incidence of acute cholangitis caused by malignant disease, sclerosing cholangitis, and non-surgical instrumentation of the biliary tract has been increasing. It is reported that malignant disease accounts for about 1-30 % of cases with acute cholangiti[17,18] (Figure 1-7).

Table 1 Etiology of acute cholangitis

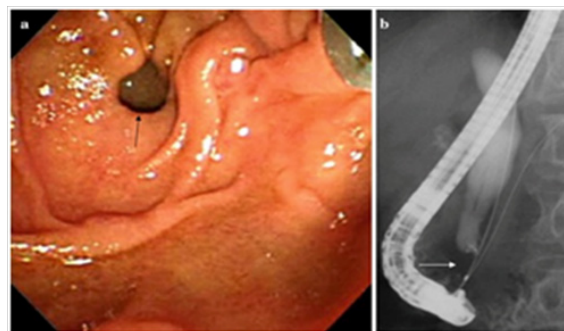| Causes	
Gallstone	Common bile duct stone (Figure 7)
	Mirizzi (Figure 6)
	Cholangiocarcinoma
Malignant biliary stricture	Gallbladder cancer
	Ampullary adenoma (Figure 5)
	Ampulary carcinoma
	Pancreatic cancer
	Metastasis to liver or portohepatic lymphonodes
	Post-surgical
Benign biliary strictures	Chronic pancreatitis
	Primary sclerosing cholangitis
	Autoimmune cholangiopathy
	Ascaris lumbricoides (Figure 3)
Parasitic	Clonorchis sinensis
	Fascicola hepatica
	Opistorchis Felineus
	Opistorchis viverrini
	Duodenal diverticula (Leimmel Syndrome (Figure 4)
Other	Hemobilia
	Sump syndrome (Obstruction by food after bilio-enteric anastomosis)
	Biliary stent obstruction (Figure 1)
	Fungal infections (Figure 2)
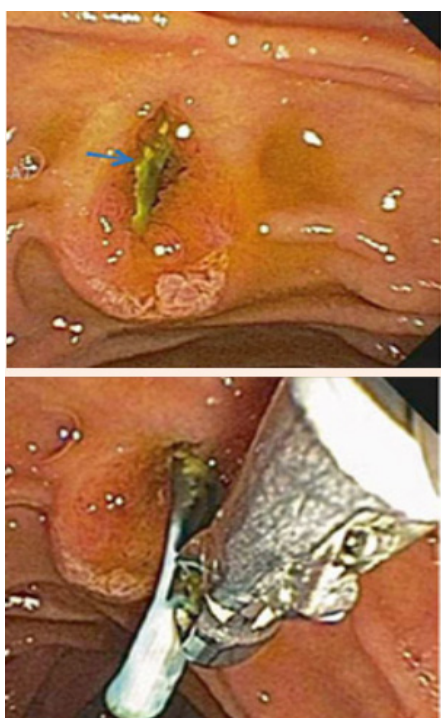
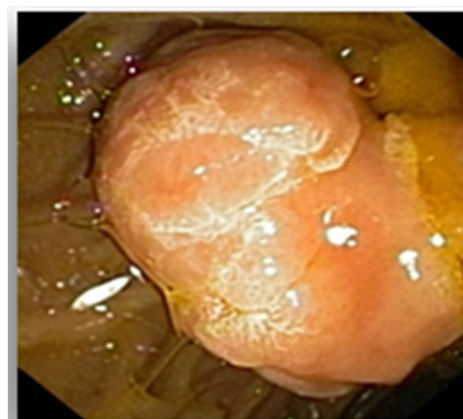**Figure 1** Plastic stent migrated into common bile duct causing biliary obstruction.

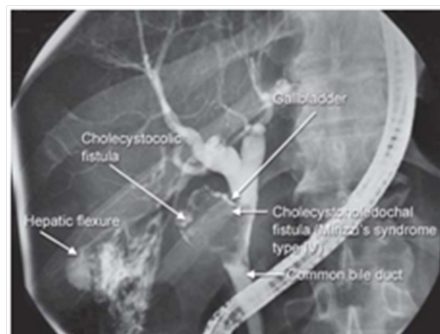**Figure 2** Fungal infection forming a "fungal ball".

 Figure 3 Ascaris infection.

Figure 4 Leimmel syndrome.

Figure 5 Ampulloma.

Figure 6 Mirizzi Syndrome.

Figure 7 Common bile duct stone.

Pathophysiology of acute cholangitis

The mechanism that cause acute cholangitis is rely on biliary obstruction that determine an increase in bile duct pressure above the normal pressure that is between 7 to 14cm H_2O. Usually this value reach 20cm H_2O but could arrive to 30cm H_2O in severe acute cholangitis. This cause a biliary-venous and lymphatic reflux because there is no basal membrane between sinuosoids and small biliary duct allowing the passage of bacteria in systemic circulation causing septic shock and death as shown in Figure 8. There are many protective mechanisms from acute cholangitis, provided in Table 2, that are divided in mechanical that is represented by Oddi sphincter and tight junction in the hepatocyte. Unfortunately the first one is removed from the sphincterotomy and the second by increased biliary pressure. The bacteriostatic mechanism such as bile flow and mucus, that prevent bacteria from adhering to the bile duct wall, are abolished from increased bile duct pressure. Finally the immunologic mechanisms such as Kupfer cell and immunoglobulin especially IgA, are compromised by the increased bile duct pressure.

Diagnosis

The diagnosis is not more based on clinical symptoms and signs (Charcot triad or Reynold pentade) as previously described because of low sensitivity accuracy (26%).[19] The diagnostic criteria are based on Tokio criteria (TG13)[19] and presented in Table 3.

Suspected diagnosis: One item in A and one in either B or C

Confirmed diagnosis: One item in A, one item in B and one item in C

Prognosis

The severity of acute cholangitis depends on the onset of organ dysfunction and response to medical treatment.

The severe acute cholangitis is characterized by the onset of organ dysfunction while moderate cholangitis is defined by the onset of the clinical signs or symptoms as summarized in Table 4.

Treatment

Generally, antibiotic therapy is given empirically to all patients with suspected acute cholangitis as early as possible and for 7 to 10days.[20] There is some evidence that once good drainage is established, 3days of antibiotic treatment may be sufficient.[21] The most common microorganism isolated from bile cultures among patients with acute cholangitis are shown in Table 5. *Escherichia Coli* and *Klebsiella* are the most common Gram-negative organisms and enterococcus for Gram-positive. It should be remembered that Anaerobes are common in patients sever ill, elderly and with severe cholangitis and sometimes in patients with biliary enteric anastomoses.[22] Finally in patients with community acquired infections, shown in Table 6, become more frequent detection of resistant bacteria such as *Klebsiella spp.* and *Pseudomonas spp.* among Gram-negative and Enterococcus spp. and *Staphylococcus* among Gram positive, therefore a probability of resistant infection must be kept in mind (Figure 9).

Table 2 Protective mechanism against acute cholangitis

Protective Mechanism	Risk Factors Compromising Protective Mechanism
Mechanical	
Sphincter of Oddi	Sphincterotomy; Biliary stent
Tight junction hepatocyte	Increased intrabiliary pressures
Bacteriostatic	
Bile flow prevent bacteria from adhering to the bile duct wall	Increased intrabiliary pressure
Bile mucus	Bile stasis
Bile salts (bacteriostatic effect)	-
Immunologic	
Kupfer cells	Increased intrabiliary pressure
Immunoglobulin (IgA)	Increased intrabiliary pressure

Table 3 Diagnostic criteria for acute cholangitis according Tokio criteria (TG13) [19]

A, Systemic Inflammation	Thresholds
A1 Fever and/or shaking chills	Body temperature > 38 °C
A2 Laboratory data: evidence of inflammatory response	WBC < 4000 or >10.000;CRP>1 mg/dl
B Cholestasis	
B1 Jaundice	T. Bilirubin > 2 mg/dL
B2 Laboratory data: abnormal liver function tests	ALP/gGT/AST /ALT > 1.5 x STD
C Imaging	
C1 Biliary dilation	
C2 Evidence of the etiology on imaging(strictire, stone, stent etc)	

Table 4 Severity assessment of acute cholangitis according to the Tokio criteria (TG13)[19]

Grade III Severe Acute Cholangitis	
Grade III severe cholangitis is associated with the onset of dysfunction in at least one of any of the following organ	
1. Cardiovascular dysfunction	Hypotension requiring dopamine>5 mcg/kg or any dose of nor epinephrine
2. Neurologic dysfunction	Disturbance of consciousness

Table continued...

Grade III Severe Acute Cholangitis	
3. Respiratory dysfunction	PAo2/Fio2 ratio < 300
4. Renal dysfunction	Oliguria, serume creatinine > 2 mg/dL
5. Hepatic dysfunction	PT/INR> 1.5
6. Hematologic dysfunction	Platelet count < 100.000/mm3
Grade II Moderate Acute Cholangitis	
Grade II Moderate cholangitis is associated with any two of the following conditions	
Abnormal WBC (>12000/mmc or < 4000/mmc)	
High fever (>39°C)	
Age (>75 y old)	
Hyperbilirubinemia (total bilirubin> 5mg/dL)	
Hypoalbuminemia (< STD x 0.7)	
Grade I Mild Acute Cholangitis	
Grade I does not meet the criteria of Grade III (severe) or Grade II (moderate) acute cholangitis at initial diagnosi	

Table 5 Common microorganisms isolated from bile cultures in patients with acute biliary infections

Isolated Microorganism from Bile Cultures	Proportion of Isolated Microorganism (%)
Gram negative	–
Escherichia Coli	31-44
Klebsiella spp	9-20
Pseudomonas spp	0.5-19
Enterobacter spp	5-9
Acinetobacter spp	-
Citrobacter spp	-
Gram positive	–
Enterococcus spp	3-34
Streptococcus spp	2-10
Staphylococcus spp	0
Anaerobes	4-20

Table 6 Common isolated microorganism from patients with acute biliary infections and community acquired infections

Isolated Microorganism	Proportion of Isolates (%) Community Acquired Infections
Gram-Negative	
Escherichia Coli	35-62
Klebsiella spp	12-28
Pseudomonas spp	4-14
Enterobacter	2-7
Acinetobacter spp	3
Citrobacter spp	2-6
Gram-positive	
Enterococcus spp	10-23
Streptococcus spp	6-9
Staphylococcus spp	2
Anaerobes	1

Timing of endoscopic biliary drainage

Timing of endoscopic biliary drainage is not evidence-based but is mainly rely on expert opinion. In a Tokio consensus conference in 200 [23] there was a good agreement between the expert about timing for severe and mild cholangitis respectively as soon as possible and after conservative treatment but there was a different approach for moderate cholangitis between Japanese and overseas expert. In fact Japanese usually performed endoscopic biliary drainage within 12hours while overseas expert after a conservative treatment. Kasbah et al.,[24] have shown that delayed and failed ERCP are associated with prolonged hospital stays and increased costs of hospitalization. Furthermore delayed ERCP is associated with composite clinical outcome (death, persistent organ failure, and/or intensive care unit stay). Older age and higher levels of bilirubin also are associated with patients' composite end-point. Lee et al reported that delayed ERCP is associated with persistent organ failure,[25] and Navaneethan et al.,[26] showed that higher ASA classification and delays ERCP are associated with adverse clinical outcomes and prolonged length of hospital stay.[26] A recent Large USA cohort study assessing 23.661 patients admitted for cholangitis who required ERCP were divided in two groups; patients admitted on the weekday (76.5%) and patients

admitted on the weekend (23.5%).This study showed that there was no weekend effect regarding to length of hospital stay, mortality or total cost of hospitalization. These results suggested that other factors in the management of cholangitis (e.g, antibiotics, intravenous fluids) contributes to outcomes.[27]
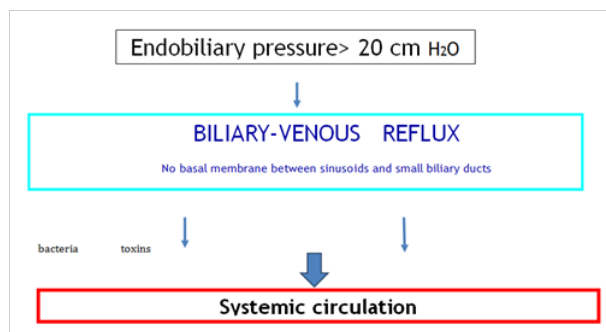

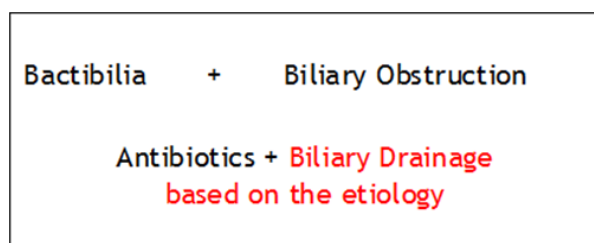**Figure 8** Pathophysiology of acute cholangitis.

Figure 9 Shows the principle of treatment in patients with acute cholangitis.
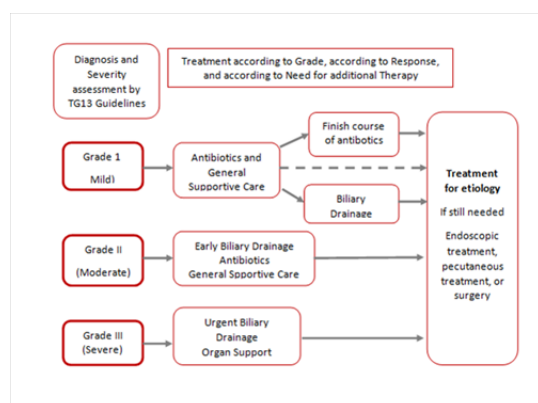

Figure 10 Algorithm of treatment approach of acute cholangitis according to the Tokio guideline.

What is the most preferable biliary drainage

Endoscopic versus percutaneous versus surgical drainage for acute cholangitis

Tokio guideline (TG13) recommended endoscopic biliary drainage for acute cholangitis (recommendation 1, level B) and suggested that percutaneous trans-hepatic biliary cholangitis drainage may be considered as alternative methods when endoscopic biliary drainage is difficult (recommendation 2, level C). Endoscopic drainage should be considered the first-choice drainage procedure because several studies have described it as less invasive than other drainage techniques.[28–32] Lai et al.,[29] have shown that endoscopic biliary drainage is associated with low mortality rate, reduced need for ventilation support and duration of ventilator support.

What procedure should be used for endoscopic biliary drainage?

Tokio guideline suggested that either ENBD or EBS may be considered for biliary drainage (recommendation 2, level B).[33] However, if ENBD is selected for the treatment of acute cholangitis, we should bear in mind that if the patient has discomfort from the trans-nasal tube placement, they are likely to remove the tube themselves, especially elderly patients. One RCT has revealed that biliary drainage is not mandatory after endoscopic clearance of the common bile duct in patients with choledocholithiasis-induced cholangitis.[34] Furthermore should be remembered that goal of treatment is based on the relief of biliary obstruction therefore any effort should be made in a single session to solve the biliary stricture regardless the aetiology.

Furthermore a trial have shown that EST in addition to biliary stent insertion is not required for successful biliary decompression in patients with severe acute cholangitis.[35] Therefore Tokio guideline suggest that EST should be determined according to the patient's condition and operator's skill (recommendation E level c). Moreover EST followed by stone removal without biliary drainage can be recommended as an alternative procedure in patients with choledocholithiasis-induced acute cholangitis (Recommendation 2 Level C). TG13 suggests that EPBD appears to be useful for treatment in patients who have coagulopathy and acute cholangitis caused by a small stone. On the other hand, theoretically, since the aim of EPBD is to preserve the function of the sphincter of Oddi, EPBD alone without biliary drainage is contraindicated for the therapy of acute cholangitis. In addition, EPBD should be avoided in patients with biliary pancreatitis. In the case of biliary drainage for therapy of acute cholangitis, skillful endoscopic technique is mandatory because long and unsuccessful procedures may lead to serious complications in critical ill patients. Therefore, endoscopists who perform endoscopic biliary drainage in these patients, should already have a high success rate of biliary cannulation including the precutting technique. An algorithm of treatment approach according to the Tokio criteria[36] is shown in Figure 10.

Acknowledgments

Conflicts of interest

Funding

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