Acute Cholecystitis

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6.1 Introduction

According to the third National Health and Nutrition Examination Survey, 6.3 million men and 14.2 million women aged 20–74 years old in the United States had gallbladder disease [1–5].

Despite the presence of several studies, meta-analysis, and guidelines, definition, diagnosis, and treatment of acute cholecystitis (AC) are still debated issues. The 2007 and 2013 Tokyo guidelines (TG) attempted to resolve these problems and to establish objective parameters for the diagnosis of AC [6, 7]. However, controversies are still present in the diagnostic value of single ultrasound (US) signs, in the timing of surgery, in the need to diagnose potential associated biliary tree stones during AC, in treatment options, in the type of surgery, in definition and management of high surgical risk patients, and in the role of cholecystostomy. In order to resolve these controversies, the World Society of Emergency Surgery (WSES) developed the 2016 WSES guidelines for acute calculous cholecystitis (ACC) [8].

6.2 Definition

Before 2007, year of the first publication of the TG for AC, there were no definite and clear diagnostic criteria for AC. The TG defined AC as:

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Table 6.1 Diagnostic criteria for acute cholecystitis according to TG

(A)	Local signs of inflammation
	1. Murphy's sign
	2. RUQ mass, pain, or tenderness
(B)	Systemic signs of inflammation
	1. Fever
	2. Elevated CRP
	3. Elevated WBC count
(C)	Imaging findings
	Imaging findings characteristic of acute cholecystitis
Definitive diagnosis	
	One item in A + one item in B + C

RUQ right upper quadrant, *CRP* C-reactive protein, *WBC* white blood cells; modified from Ref. 7

an acute inflammatory disease of the gallbladder, often attributable to gallstones, but many factors, such as ischemia, motility disorders, direct chemical injury, infections by microorganism, protozoon and parasites, collagen disease, and allergic reaction are also involved [9].

AC is caused by the presence of gallstones in almost the totality of cases. According to the TG, a diagnosis of AC can be made when all these three proposed criteria are satisfied [7, 10] (see Table 6.1):

1. The presence of local inflammation, represented by the presence of right upper quadrant pain and Murphy's sign; this sign has a high specificity (79–96%) but a poor sensitivity (50–65%): although it is the most famous and considered pathognomonic sign for gallbladder diseases, it cannot be used as a single item in making diagnosis [7].
2. The presence of systemic inflammation, represented by fever or elevated white blood cell count or C-reactive protein level [7].
3. Imaging findings characteristic of AC [7].

According to WSES guidelines, there is no single clinical or laboratory finding with sufficient diagnostic accuracy to establish or exclude AC, and only a combination of detailed history, complete clinical examination, laboratory tests, and imaging investigation may strongly support the diagnosis of AC, although the best combination is not yet known [8].

6.3 Imaging

US is the gold standard imaging technique for AC because of its lower cost, better availability, and lack of invasiveness [8, 11]. The TG recommended it as the first step in diagnosis too, and the diagnostic signs were identified as an enlarged gallbladder, a thickened wall greater than 5 mm, the presence of stones, the debris echo, and the US Murphy's sign. In the study by Hwang et al. [12], a sensitivity of 54% and a specificity of 81% were reported by using the combination of sonographic

Murphy's sign, gallbladder wall thickening greater than 3 mm, pericholecystic fluid collection as major criteria, and hepatic biliary dilation and gallbladder hydrop as minor criteria. In the study by Borzellino et al. [13], distension of the gallbladder, wall edema, and pericholecystic fluid collection were adopted as the criteria for the diagnosis of AC. The presence of at least one of these three criteria from US resulted in a sensitivity of 83.7% and a specificity of 47.7%. Therefore US alone seems to be of limited utility to diagnose or exclude the diagnosis of AC.

Diagnostic accuracy of computed tomography (CT) is poor, while diagnostic accuracy of magnetic resonance imaging (MRI) is comparable to US, but it is poorly applicable in urgency contest. Hepatobiliary iminodiacetic acid scan (HIDA scan) has the highest sensitivity and specificity for AC, although its scarce availability, long time required to perform the test, and exposure to ionizing radiation limit its use [8].

6.4 Acute Calculous Cholecystitis (ACC)

In high- and intermediate-income countries, 10–15% of the adult population are affected by gallstones, and AC occurs in 10–20% of untreated patients [8].

6.4.1 Classification

The TG suggested a classification for AC, structured in three different levels of severity, based on the characteristic of the acute inflammatory process [7]:

1. Grade III, *severe AC*: an AC associated with organ dysfunction.
   (a) Cardiovascular dysfunction: Hypotension with dopamine >5 μg/kg per min or norepinephrine, any dose
   (b) Neurological dysfunction: Decreased level of consciousness
   (c) Respiratory dysfunction: PaO_2/FiO_2 ratio < 300
   (d) Renal dysfunction: Oliguria, creatinine > 2.0 mg/dL
   (e) Hepatic dysfunction: PT-INR > 1.5
   (f) Hematological dysfunction: Platelet count < 100,000/mm^3
2. Grade II, *moderate AC*, associated with any one of the following conditions:
   (a) Elevated white blood cell count (>18,000/mm^3)
   (b) Palpable tender mass in the right upper abdominal quadrant
   (c) Duration of complaints >72 h
   (d) Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)
3. Grade I, *mild AC*, does not meet the criteria of "Grade III" or "Grade II" AC: Grade I can also be defined as AC in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.

This clinical classification was the first attempt to create an international grading system in order to standardize data and patients characteristics and to choose the best treatment option. However these criteria are based mainly on the characteristics of the local acute inflammatory process taking little account of the patient's clinical characteristics and risk factors [14].

6.4.2 Common Bile Duct Stones Associated to Acute Calculous Cholecystitis

In patients with ACC, the presence of a concomitant lithiasis of the common bile duct (CBD) is reported in literature ranging from 8.7% to 25% [15–17]. Liver biochemical tests, including ALT, AST, bilirubin, ALP, and gamma-glutamyl transferase (GGT), should be performed in all patients with AC to assess the risk for CBD lithiasis [8]. The treatment of CBD stones can be performed before, during, or after the cholecystectomy: if performed before, the suspected choledocholithiasis is one of the major factors implicated in the delaying of surgery. The TG didn't analyze this problem, while the ASGE (American Society for Gastrointestinal Endoscopy) guidelines for the choledocholithiasis are a very useful tool, even if not specific for ACC [18]. These guidelines created a stratification for the risk of choledocholithiasis (high, >50%; intermediate, 10–50%; low, <10%) based on moderate, strong, and very strong predictive factors (see Table 6.2). As a consequence, the choledocholithiasis management suggested was based on the predicted risk: in case of low risk, no further investigations were recommended; in case of high risk, ERCP before surgery was suggested; and in case of intermediate risk, preoperative endoscopic US or MRCP or intraoperative cholangiography or a laparoscopic US of the CBD was suggested depending on the local expertise and availability; if positive, ERCP was recommended (see Fig. 6.1).

Table 6.2 ASGE predictive factors and risk classes for choledocholithiasis

Predictive factor for choledocholithiasis	
Very strong	Evidence of CBD stone at abdominal ultrasound
Strong	Common bile duct diameter > 6 mm (with gallbladder in situ)
	Total serum bilirubin > 4 mg/dL
	Bilirubin level 1.8–4 mg/dL
Moderate	Abnormal liver biochemical test other than bilirubin
	Age older than 55 years
	Clinical gallstone pancreatitis
Risk class for choledocholithiasis	
High	Presence of any very strong
Low	No predictors present
Intermediate	All other patients

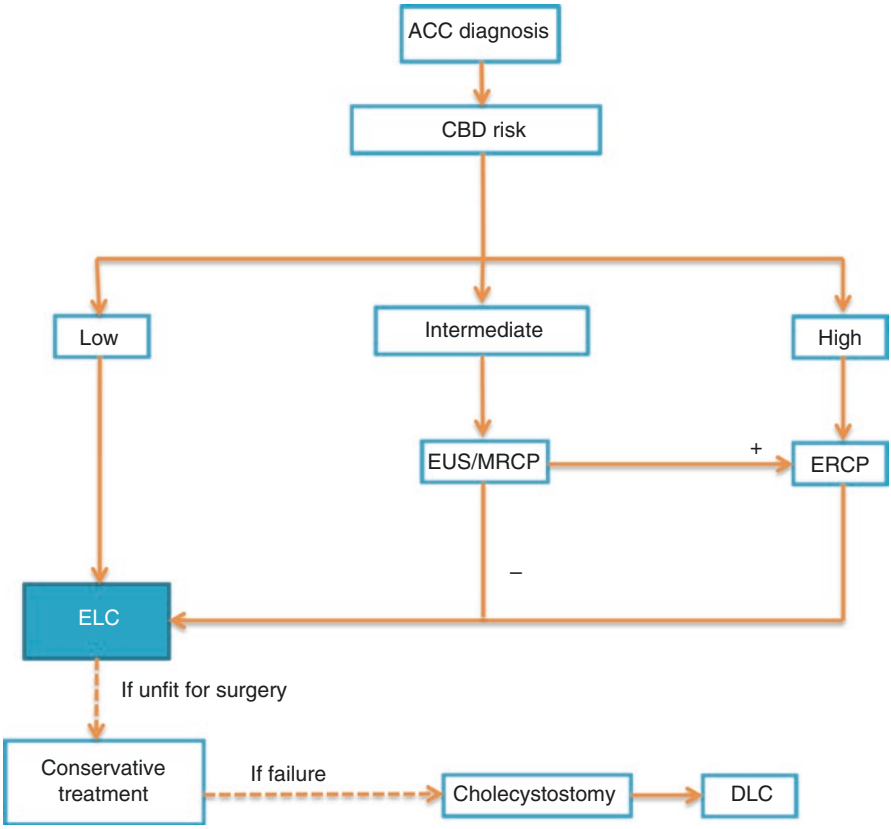

Fig. 6.1 Comprehensive WSES algorithm for the treatment of acute calculous cholecystitis. *ACC* acute calculous cholecystitis, *CBD* common bile duct calculus, *ELC* early laparoscopic cholecystectomy, *ERCP* endoscopic retrograde cholangiopancreatography, *EUS* endoscopic ultrasound, *MRCP* magnetic resonance cholangiopancreatography, *DLC* delayed laparoscopic cholecystectomy

6.4.3 Treatment

6.4.3.1 Surgical Therapy

In the second half of the 18th century, AC started to be treated by Petit with a cholecystostomy with a permanent biliary fistula; at the end of the 19th century, precisely in 1882, the first open cholecystectomy was performed by Langenbuch, and the removal of gallbladder during the initial hospitalization became the gold standard for symptomatic cholelithiasis [19]. During the prelaparoscopic era, several studies found that the better treatment was early open cholecystectomy within 7 days from the onset of symptoms, also in order to reduce rehospitalization for the high rate of recurrence [20, 21]. With the advent of laparoscopy, laparoscopic cholecystectomy (LC) became the gold standard technique. During these years, a lot of reports, case series, and RCTs have been published in order to define which is the

better timing for laparoscopic cholecystectomy in AC, early (ELC) or delayed (DLC).

Tokyo Guidelines

The TG suggested a treatment flowchart based on the clinical classification of AC [22]:

(a) Grade I AC: antibiotic therapy plus ELC is recommended.
(b) Grade II AC: the TG recommend to treat conservatively the acute inflammation with antibiotic therapy and program DLC; a percutaneous gallbladder drainage (percutaneous cholecystostomy, PC) is recommended if antibiotic therapy fails; surgery is recommended only if essential in emergency. ELC in this setting is contemplated only if advanced laparoscopic expertise is available.
(c) Grade III AC: PC plus antibiotic therapy is indicated.

In the TG the treatment indications were based more on the acute inflammatory process than on the patient clinical conditions. However, the advocated association between inflammatory status and difficulty of surgery was supported by weak evidences. Furthermore, the indications to PC in TG were not clear [23] because it was recommended in Grade III AC and sometimes in Grade II AC [22], but also as a safe option in high-risk patients with less severe AC who were considered poor surgical candidates or when a difficult dissection was encountered. Lastly the TG didn't give any indications on CBD stone management.

WSES Guidelines

WSES proposed an evidence-based flowchart for the treatment of AC [8] (Fig. 6.1).

According to WSES guidelines, surgery is recommended as a decisive treatment during the first hospital admission unless contraindicated. All the cholecystectomies should be started with laparoscopic technique unless there are contraindications; for the optimal timing for surgery, evidences show that there is not a strict limit, so ELC should be performed on an "as soon as possible" basis. If the patient is unfit for surgery, he/she should receive a conservative medical treatment with antibiotic. In patients where surgery is not indicated, if there isn't a resolution of the clinical setting after 48 h of medical therapy, PC with the percutaneous transhepatic technique is indicated, and a later surgical evaluation after 60 days from discharge for possible cholecystectomy should be planned.

Regarding the assessment of the risk for choledocholithiasis, after an evaluation for the presence of peritonitis, a condition that leads the patient to an emergency operation, WSES guidelines suggest to consider the ASGE guidelines. With a low risk, if the patient is eligible for surgery, ELC should be performed as soon as possible. If the patient is unfit for surgery, he/she should receive antibiotic therapy and eventually PC, if the medical treatment is ineffective after 48 h. Patient at high risk for choledocholithiasis should undergo directly ERCP or, if ERCP is ineffective, a surgical exploration of the CBD. Patients with intermediate risk have to be evaluated with MRCP or endoscopic US, based on the availability of the staff, to select patients who should receive ERCP. Either patients at high risk or those at

intermediate one, after diagnostic evaluation, if fit for surgery, should receive ELC or should be treated conservatively with antibiotic therapy if unfit [8].

Patients Selection for Surgery

In AC the severity of clinical setting and its life-threatening potential are strongly determined by the general status of the patient. For example, the patient's age above 80 and the coexistence of diabetes mellitus are major risk factors for worse clinical outcome, morbidity, and mortality. Currently, there is no evidence of the existence of any accurate scores in identifying patient's risk in surgery for AC in order to declare a patient fit or unfit for ELC. The only available risk assessment scores comparison (ASA vs APACHE II vs POSSUM) is limited to the perforated AC, and it found a significant association of the three scores with morbidity and mortality. APACHE II seems to be the best risk predictor [24], but it is built to predict morbidity and mortality in patients admitted to the ICU: its use as a preoperative score should be considered as an extension usage from the original concept. Therefore, prospective and multicenter studies to compare different risk factors and scores are necessary [8].

Timing for Surgery

Several randomized controlled trials have investigated ELC versus DLC [25–33]. The problem is that early and delayed laparoscopic cholecystectomies have been defined differently in different trials. In general, ELC has been defined variably as performed in patients with symptoms from less than 72 h or from less than 7 days but within 4–6 days from diagnosis. This roughly translates to 10 days from onset of symptoms. The DLC is defined variably as performed between 7 days to 45 days and performed at least 6 weeks after initial diagnosis. According to several meta-analyses [34–37], ELC and DLC aren't different in terms of conversion rate to open cholecystectomy or in terms of CBD injury, but a significant decrease in total hospital stay and a more cost-effective approach were found in the ELC group.

A great debate still exists regarding the best timing for ELC: historically the limit of 72 h for its performance has been reported. However it is not always clear if it is considered from the onset of symptoms or from hospital admission. Despite the presence of large studies showing that better results could be obtained with a limit of 48 h from admission [38, 39], other studies cannot individuate an exact time limit [40–43]. However, it should be noted that earlier surgery is associated with shorter hospital stay and fewer complications, and it is cost-effective [8, 38, 44–47].

WSES guidelines stated that ELC is preferable to DLC, and ELC should be performed as soon as possible up to 10 days from the onset of symptoms [8].

Conversely ELC should not be offered for patients beyond 10 days from the onset of symptoms unless there is worsening peritonitis or sepsis warrants an emergency surgical intervention. In people with more than 10 days of symptoms history, delaying cholecystectomy after 45 days is better than immediate surgery [8].

Despite the presence of these evidences, up to 80% of patients with AC do not receive the definitive surgical treatment during the first hospital admission [48–52], increasing costs and hospitalization without clinical advantages.

Type of Surgery

According to both Tokyo and WSES guidelines in AC, a laparoscopic approach should initially be attempted except in case of absolute anesthesiology contraindications or septic shock [8]. Laparoscopic cholecystectomy (LC) for AC is safe, feasible, with a low complication rate, and associated with shorter hospital stay [53–62]. Among high-risk patients, in those with Child A and B cirrhosis, in those with advanced age > 80, or in pregnant women, laparoscopic cholecystectomy is feasible and safe [8]. Indication to LC in patients with Child C cirrhosis is not clear [63–66], and as a first recommendation, cholecystectomy should be avoided in these patients, unless clearly indicated, such as in AC not responding to antibiotics [66].

According to WSES guidelines, subtotal cholecystectomy (laparoscopic or laparotomic) is a valid option for advanced inflammation, gangrenous gallbladder, or in any situations in which anatomy is difficult to recognize and main bile duct injuries are more likely.

Furthermore in case of local severe inflammation, adhesions, bleeding in Calot's triangle, or suspected bile duct injury, conversion to open surgery should be strongly considered.

6.4.3.2 Antibiotic Therapy

Although surgery is the gold standard in the treatment of AC, antibiotics are an important component in its management, in association with ELC or DLC for fit-for-surgery patients or alone for high-risk patients [67, 68].

In association with surgery, antibiotics are always recommended in complicated cholecystitis and in delayed management of uncomplicated cholecystitis. Patients with uncomplicated cholecystitis can be treated without postoperative antibiotics when the focus of infection is controlled by cholecystectomy. In complicated cholecystitis, the antimicrobial regimens depend on presumed pathogens involved and risk factors for major resistance patterns [8]. Organisms most often involved in biliary infections are the gram-negative aerobes, *Escherichia coli* and *Klebsiella pneumoniae*, and anaerobes, especially *Bacteroides fragilis* [69, 70]. In immunosuppressed patients, enterococcal infection should always be presumed and treated [71]. Healthcare-related infections are commonly caused by more resistant strains. For these infections, complex regimens with broader spectra are recommended as adequate empiric therapy appears to be a crucial factor affecting postoperative complications and mortality rates, especially in critically ill patients [71]. In Table 6.3 are reported antimicrobial regimen suggested by WSES for AC.

However, microbiological analyses are helpful in designing targeted therapeutic strategies for individual patients, mostly in patients at high risk for antimicrobial resistance [8].

6.4.3.3 Percutaneous Cholecystostomy

Gallbladder drainage decompresses the infected bile or pus in the gallbladder, removing the infected collection without removing the gallbladder. The removal of the infected material, in addition to antimicrobial therapy, can result in a reduced inflammation with an improvement of the clinical condition [8]. The TG considered

Table 6.3 Antimicrobial regimens suggested for acute calculous cholecystitis

Community acquired	
Beta-lactam/beta-lactamase inhibitor combination-based regimens	Amoxicillin/clavulanate (in stable patients) Ticarcillin/clavulanate (in stable patients) Piperacillin/tazobactam (in unstable patients)
Cephalosporin-based regimens	Ceftriaxone + metronidazole (in stable patients) Cefepime + metronidazole (in stable patients) Ceftazidime + metronidazole (in stable patients) Cefozopran + metronidazole (in stable patients)
Carbapenem-based regimens	Ertapenem (in stable patients) Imipenem/cilastatin (only in unstable patients) Meropenem (only in unstable patients) Doripenem (only in unstable patients)
Fluoroquinolone-based regimens (in case of allergy to beta-lactams)	Ciprofloxacin + metronidazole (only in stable patients) Levofloxacin + metronidazole (only in stable patients) Moxifloxacin (only in stable patients)
Glycylcycline-based regimen	Tigecycline (in stable patients if risk factors for ESBLs)
Healthcare associated	
In stable patients	Tigecycline + piperacillin/tazobactam
In unstable patients	Imipenem/cilastatin ± teicoplanin Meropenem ± teicoplanin Doripenem ± teicoplanin

the gallbladder drainage as mandatory in severe grade AC and also suggested its use in the moderate grade if conservative treatment fails. Furthermore the TG stated PC as an effective option in critically ill patients, especially in elderly patients and in patients with complications. However the role of PC is difficult to be determined because the "high-risk patients" definition is still unclear.

According to WSES guidelines, gallbladder drainage, and in particular percutaneous transhepatic gallbladder drainage (PTGBD), together with antibiotics, can convert a septic cholecystitis into a non-septic condition. It could be considered as a possible alternative to surgery after the failure of conservative treatment, after a variable time of 24–48 h, in a small subset of patients unfit for emergency surgery due to their severe comorbidities [8]. However the level of evidence is poor [8]. At

the moment a randomized controlled trial comparing PC with ELC in critically ill patients (APACHE score 7–14) with AC (the CHOCOLATE trial) is ongoing [72]: this will clarify the real role of PC (1a).

Mortality following the procedure is high (15%) but generally it is related to the severity of the underlying disease process [23]. The need for delayed cholecystectomy after PC also remains controversial: because approximately 40% of patients will have recurrent biliary tract disease within 1 year following PC [73], the surgical approach could be considered as an option.

6.5 Acute Acalculous Cholecystitis (AAC)

AAC is an acute inflammatory disease of the gallbladder without evidence of gallstones and represents 2–15% of all AC. The first case was reported in 1844 by Ducan et al. This disease is burdened with a higher mortality than AC that ranges from 10% to 90% (in opposite to 1% of AC) that is often related to the delay in diagnosis [74].

6.5.1 Pathogenesis and Diagnosis

AAC occurs often in hospitalized patients and arises in 0.2–0.4% of all critically ill patients. It is due to two main mechanisms: ischemia and bile stasis. There are many possible causes: shock, hypovolemia, heart failure, myocardial ischemia, dehydration, diabetes mellitus, abdominal vasculitis, malignant diseases, abdominal surgery, cholesterol embolization, sepsis with visceral arterial hypoperfusion, and cerebrovascular disease. Moreover, also fever, fasting, and dehydration alone (typical conditions of the ICU patients) can result in concentration of biliary salts, bile stasis, and consequent AAC [74]. Diagnosis is often difficult because it can be masked by the patient's concomitant or primary diseases [75]. Some authors emphasized the difficulty of differential diagnosis from cardiovascular disease due to symptom overlapping. Ultrasound plays a key role in AAC diagnosis. Complications of AAC, such as empyema, gangrene, abscess, and perforation are more common than in ACC with an incidence ranging from 37% to 81% [74–76].

6.5.2 Treatment

Although cholecystectomy is generally the gold standard in any infectious disease of the gallbladder, there is only a low level of evidence about a surgical or nonsurgical approach to critically ill patients with AAC [75]. The treatment decision depends mainly on the patient's comorbidities and conditions. In low-risk patients, when the risks under general anesthesia are low, a laparoscopic approach should be the preferred surgical intervention. However, in critically ill patients with multiple comorbidities, PC provides better outcomes with lower cost, lower morbidity, and lower mortality than laparoscopic and open cholecystectomy [76]. PC is safe, rapid, and

highly efficacious in treating AAC, and it can be performed at the bedside under local anesthesia. It can represent a definitive treatment or a bridge until cholecystectomy may be safely performed. PC is contraindicated in cases of gangrene or gallbladder perforation [76]. Regarding antimicrobial therapy, these critically ill patients are more prone to infections with multiresistant bacteria [75].

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