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ADVANCES IN SURGERY

Acute Cholecystitis
Early Versus Delayed Surgery

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Keywords

• Acute cholecystitis • Cholecystectomy • Timing • Surgery • Laparoscopic

Key points

- Laparoscopic cholecystectomy is widely established as the standard operation in acute cholecystectomy.
- Valid data from several prospective studies including a recent large randomized multicenter trial are available that demonstrate that early cholecystectomy is associated with less morbidity, a shorter length of hospital stay, and lower total hospital costs compared with delayed cholecystectomy after a conservative treatment period with antibiotics.
- Early cholecystectomy within 24 hours of hospital admission is the therapy of choice in patients fit for surgery, and this should be implemented as the standard treatment algorithm for this condition.

INTRODUCTION

Acute cholecystitis is a common disease in the Western World and has a high socioeconomic impact [1]. Laparoscopic or eventually open cholecystectomy is usually recommended to patients with a first attack of acute cholecystitis, because the risk of developing subsequent episodes of cholecystitis is high. The optimal timing of surgery for acute cholecystitis remains controversial: early surgery shortly after hospital admission versus delayed surgery after an initial conservative management with antibiotics for complete resolution of inflammation. This article provides an overview of the management of patients with acute cholecystitis, with a focus on the timing of cholecystectomy.

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PATHOGENESIS

Acute cholecystitis is defined as an inflammation of the wall of the gallbladder. In many cases an impacted gallstone in the gallbladder infundibulum or in the cystic duct is the cause for the inflammatory process [2]. The continuing mucin production from the gallbladder's epithelium in combination with the impacted gallstone results in gallbladder distension and edema with acute inflammation. This can eventually result in micro- and macrocirculatory perfusion deficits with subsequent ischemia and necrosis. The acute inflammation may be complicated by secondary infection. Infection may be ascending from the bile duct or via the lymphatic or vascular system and occurs in the majority of patients with acute cholecystitis. Gram-negative bacteria of gastrointestinal origin, such as *Klebsiella* subspecies, *Enterobacter*, and *Escherichia coli*, or anaerobes are the most common pathogens [3,4].

Acute calculous cholecystitis can be found at any age and is a typical complication of cholelithiasis. However, the incidence increases with age, with a peak between 70 and 75 years. Gallstones can be found in 66% of the population at an age of more than 70 years, but they are asymptomatic in the majority of patients. Patients with symptomatic cholecystolithiasis will develop acute cholecystitis more frequently compared with asymptomatic patients (10%–20% vs 5%). About 60% of patients with cholecystitis are women due to a three-fold higher incidence of cholecystolithiasis in women compared with men [5]. However, men tend to have more severe cholecystitis [6].

Acute acalculous cholecystitis is a less common version of cholecystitis that occurs most often in critically ill patients. Risk factors are generalized sepsis, major trauma, prolonged low output after cardiac operations, burns, or protracted recovery from major operations [7].

CLINICAL MANIFESTATION

Severe, right upper quadrant or epigastric pain is the guiding symptom of acute cholecystitis. The pain may radiate to the subscapular area and may aggravate during movement. Patients often report a preceding episode of biliary colic with intermittent, self-limiting bouts of abdominal pain. The visceral pain character blends over into a parietal pain over time. Acute cholecystitis is often associated with fever, loss of appetite, nausea, and vomiting. Fever and leukocytosis are not present in cases of uncomplicated biliary colic. Shivering attacks and a septic clinical course indicate a possible gallbladder empyema.

Clinical examination reveals tenderness on palpation of the right upper abdominal quadrant. One may find a Murphy sign (inspiratory arrest on palpation), which has high sensitivity and specificity. A palpable gallbladder hydrops can be found in about a quarter of patients. Laboratory findings are leukocytosis, an increase of C-reactive protein, a mild increase of bilirubin in about 50% of patients, and slightly elevated transaminases in about a quarter of patients [8]. According to the Tokyo guidelines [9], a combination of clinical, laboratory, and imaging findings will provide the basis for a suspected or definite diagnosis of acute cholecystitis (Box 1).

Box 1: Diagnostic criteria for acute cholecystitis

A. Local signs of inflammation
   1. Murphy sign
   2. Right upper quadrant mass/pain/tenderness

B. Systemic signs of inflammation
   1. Fever
   2. Elevated C-reactive protein
   3. Abnormal white blood cell count

C. Imaging findings: imaging findings characteristic of acute cholecystitis

Suspected diagnosis: 1 item in A + 1 item in B.
Definite diagnosis: 1 item in A + 1 item in B + C.
Acute hepatitis, other acute abdominal diseases, and chronic cholecystitis should be excluded.

Data from Yokoe M, Takada T, Strasberg SM, et al. New diagnostic criteria and severity assessment of acute cholecystitis in revised Tokyo guidelines. J Hepatobiliary Pancreat Sci 2012;19(5):578–85.

IMAGING

Abdominal ultrasound is the primary imaging modality for assessing patients with suspected acute cholecystitis. Ultrasound is in general readily available, cost-effective, and highly sensitive and specific, with an overall accuracy rate of 90% to 95% [10,11]. Typical signs of acute cholecystitis in ultrasound are gallbladder wall thickening (>4 mm), pericholecystic fluid, gallstones, or direct tenderness when the probe is pushed against the gallbladder (ultrasonographic Murphy sign). Computed tomography (CT) can also help to diagnose acute cholecystitis and provides more detailed information, particularly in patients whose symptoms suggest complications of cholecystitis or an alternative diagnosis. CT findings of acute cholecystitis were reported as gallbladder distention, gallbladder wall thickening, pericholecystic fat density, pericholecystic fluid collection, subserosal edema, and high-attenuation gallbladder bile [12]. However, CT is less sensitive than ultrasound for diagnosing acute cholecystitis [13].

Hepatobiliary scintigraphy has been described to be a useful study in selected patients when the diagnosis is uncertain. Tracer-labeled derivates of aminodiacetic acid, which are taken up by hepatocytes and secreted in the bile, are used to visualize biliary function. A normal scan delineates the biliary tree, including the gallbladder, and shows prompt emptying of the tracer into the duodenum. Nonvisualization of the gallbladder is consistent with acute cholecystitis. In patients with acute cholecystitis, hepatobiliary scintigraphy had higher specificity and accuracy than ultrasonography [14,15]. Despite its potential diagnostic value, this expensive and time-consuming imaging technique has no relevance in the diagnosis of acute cholecystitis at the authors' institution.

SEVERITY OF ACUTE CHOLECYSTITIS AND TREATMENT

After a patient has been diagnosed with acute cholecystitis, the severity of the disease should be determined to start a severity-adapted specific therapy. The revised Tokyo guidelines [9] describe 3 grades of severity (Box 2). Grade 3 or severe cholecystitis is associated with dysfunction of an organ or an organ system. Frequently, a severe local inflammatory reaction requires an emergency cholecystectomy. In severely ill patients or patients who cannot undergo general anesthesia, a percutaneous cholecystostomy should be performed. Organ functions need to be supported during patients' therapy in an intensive care unit [16]. A Dutch randomized multicenter trial is currently comparing laparoscopic cholecystectomy versus percutaneous cholecystostomy in high-risk surgical patients with acute calculous cholecystitis (CHOCOLATE Trial (Laparoscopic cholecystectomy versus percutaneous cholecystostomy in acute calculous cholecystitis in high risk patients), Netherlands Trial Registry [NTR]: NTR2666) [17].

Grade 2 or moderate acute cholecystitis is defined by any of the following conditions: elevated white blood cell count greater than 18,000/mm^3, palpable

Box 2: Severity assessment criteria for acute cholecystectomy

Grade 3 (severe) acute cholecystitis is associated with dysfunction of any of the following organs/systems

1. Cardiovascular dysfunction: hypotension requiring treatment with dopamine $\geq$5 μg/kg/min, or any dose of norepinephrine
2. Neurologic dysfunction: decreased level of consciousness
3. Respiratory dysfunction: Pa_{O_2}/Fi_{O_2} ratio <300
4. Renal dysfunction: oliguria, creatinine >2.0 mg/dL
5. Hepatic dysfunction: prothrombin time and international normalized ratio (PT-INR) >1.5
6. Hematological dysfunction: platelet count <100,000/mm^3

Grade 2 (moderate) acute cholecystitis is associated with any of the following conditions

1. Elevated white blood count (18,000/mm^3)
2. Palpable tender mass in the right upper abdominal quadrant
3. Duration of complaints longer than 72 h
4. Marked local inflammation (gangrenous cholecystitis, pericholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)

Grade 1 (mild) acute cholecystitis does not meet the criteria of grade 3 or grade 2 acute cholecystitis. Grade 1 can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure

Data from Yokoe M, Takada T, Strasberg SM, et al. New diagnostic criteria and severity assessment of acute cholecystitis in revised Tokyo guidelines. J Hepatobiliary Pancreat Sci 2012;19(5):578–85.

tender mass in the right upper abdominal quadrant, duration of complaints greater than 72 hours, or marked local inflammation [9]. Early laparoscopic or open cholecystectomy should be performed. In case of severe local inflammation, which would make early cholecystectomy more complicated, the Tokyo guidelines from 2007 recommend percutaneous or open cholecystostomy to facilitate an elective interval cholecystectomy at a time when the acute inflammatory process declined [16]. At present, the role of cholecystostomy in moderate cholecystitis is assumed to be low.

Grade 1 or mild acute cholecystitis does not meet the criteria of grade 3 or grade 2 acute cholecystitis. Grade 1 can be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure [9]. Early laparoscopic cholecystectomy is deemed to be the optimal therapy [16].

The Tokyo guidelines quote systemic antibiotics as a standard therapy in acute cholecystitis [18]. However, these guidelines have to be regarded as nonevidence-based, because randomized controlled trials on this issue are barely available. Patients with mild cholecystitis, relatively slight abdominal pain, and mild inflammatory parameters may possibly be treated without antibiotics. This recommendation was confirmed by a recent randomized controlled trial in patients with mild calculous cholecystitis [19]. When cholecystectomy has been performed, antibiotic therapy should be stopped within 24 hours, unless there are signs of infection outside of the gallbladder wall [20].

TIMING OF CHOLECYSTECTOMY

One of the most relevant questions in the therapy of acute cholecystitis is the optimal timing of cholecystectomy [21]. Mainly 2 approaches with opposing rationality are pursued, and each is supported by the results of various studies; early surgery versus an initial conservative treatment with antibiotics for complete resolution of inflammation, followed by delayed laparoscopic cholecystectomy several weeks later [22]. In daily practice, specialization and preference of the physician at first patient contact and country-specific treatment algorithms seem to influence the approach [23].

Delayed surgery is based on the assumption that affected inflammatory tissue is more vulnerable to surgical interventions and leads to an increased risk of surgical complications. Therefore, during its early years, laparoscopic cholecystectomy was contraindicated in acute cholecystitis [24]. With increasing experience and expertise in laparoscopic cholecystectomy, the concerns about performing the operation in inflamed tissue has become less relevant. More recent prospective studies do not support the necessity of conservative pretreatment to overcome the acute inflammatory response, and laparoscopic cholecystectomy in this setting has been shown to be safe and effective [25–27]. Indeed, the waiting period may be associated with higher morbidity [28]. A recent population-based analysis of 4113 patients with acute cholecystitis demonstrated that immediate surgery was associated with

significant advantages in conversion/reoperation rates, postoperative complications, and length of postoperative hospital stay compared with delayed cholecystectomy 1 to 6 days after hospital admission [29]. Meta-analyses have shown that there is no difference between the 2 approaches in terms of bile duct injury, operation time, or conversion rate, whereas total hospital stay is significantly shortened by early cholecystectomy [22,23,30–32]. The Cochrane meta-analysis by Gurusamy and colleagues [30] was a cost-utility analysis that showed that early laparoscopic cholecystectomy in acute cholecystitis is less costly (savings of £820 per patient) and results in better quality of life than initial conservative treatment followed by delayed surgery. However, despite numerous studies and meta-analyses, the controversy regarding the optimal timing of cholecystectomy in acute cholecystectomy has remained because of several issues:

Available prospective studies had mostly enrolled only few patients.
The definition of early cholecystectomy varied.
Antibiotic regimens for the conservative approach were not standardized.

Most recently, the results of the largest prospective, randomized, multicenter study to date comparing immediate cholecystectomy within 24 hours of hospital admission versus delayed elective surgery at 7 to 45 days after conservative treatment with antibiotics were published [33]. That study clearly favors immediate laparoscopic cholecystectomy as the therapy of choice for acute cholecystitis in operable patients. Six hundred eighteen patients from 35 study centers in Germany and Slovenia who showed clinical signs and symptoms of acute cholecystitis (according to the Tokyo guidelines) combined with proven cholecystolithiasis (stones/sludge) or ultrasonographic signs of cholecystitis were randomized when laparoscopic cholecystectomy was possible within 24 hours after presentation of the patient. For infection, all patients were treated with the third-generation fluoroquinolone moxifloxacin for at least 48 hours.

In that study, morbidity within 75 days after inclusion into the study, which was the primary endpoint of the study, was significantly lower in the immediate surgery group compared with the delayed cholecystectomy group (11.8% vs 34.4%, respectively). Conversion rate to open surgery and mortality rate, two of the secondary endpoints, did not differ significantly between the groups (Table 1). Importantly, mean length of hospital stay (5.4 days vs 10.0 days, respectively) and total hospital costs (€2919 vs €4262, respectively) were significantly lower in the immediate cholecystectomy group. Based on the results of this large, prospective, randomized, multicenter trial, it is obvious that patients with acute cholecystitis should be operated laparoscopically within 24 hours after admission, if their physical fitness allows surgery. The initial conservative approach followed by delayed surgery is associated with a measurable risk so that, that even using an effective antibiotic treatment, signs and symptoms of acute cholecystitis may not resolve or may recur shortly, eventually leading to prolonged hospitalization or rehospitalization, surgery under more difficult conditions, and higher costs [33].

Table 1
Outcome by treatment groups (intention-to-treat analysis)

Secondary efficiency outcomes	Early laparoscopic cholecystectomy (n = 304)	Delayed laparoscopic cholecystectomy (n = 314)	*P*
Morbidity score on day 75, mean (95% confidence interval [CI])	0.53 [0.10–0.96]	1.12 [0.66–1.58]	<.001
Conversion rate to open surgery, n (%) [95% CI]	30 (9.9) [6.5–13.2]	33 (11.9) [8.1–15.7]	.44
Adverse events, n (%) patients [95% CI]	43 (14.1) [10.2–18.1]	127 (40.4) [35.0–45.9]	<.001
Mortality rate, n (%)	1 (0.3)	1 (0.3)	.98
Total hospital stay, mean (interquartile range) [95% CI], d	5.4 (4–6) [5.08–5.71]	10.03 (7–12) [9.36–10.69]	<.001
Total hospital costs, mean (interquartile range) [95%, CI], €	2919 (2651–2651) [2812–3026]	4262 (3021–4724) [4029–4494]	<.001

Modified from Gutt CN, Encke J, Koninger J, et al. Acute cholecystitis: early versus delayed cholecystectomy, a multicenter randomized trial (ACDC Study, NCT00447304). Ann Surg 2013;258:385–93.

OPEN VERSUS LAPAROSCOPIC CHOLECYSTECTOMY

Laparoscopic cholecystectomy is the gold standard in the therapy of symptomatic cholecystolithiasis and has gained broad acceptance within the 30 years [34]. Initially, acute cholecystitis was seen as a contraindication for laparoscopic cholecystectomy. With improvements in laparoscopic operation techniques and increasing experience of surgeons with minimal invasive surgery, laparoscopic cholecystectomy became the preferred therapy of acute cholecystitis, as stated by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines [35]. A prerequisite is the experienced surgeon with this technique [36].

Randomized controlled trials that compare open and laparoscopic cholecystectomy for acute cholecystitis show predominantly an advantage for laparoscopic surgery [37,38] or comparable results with the 2 techniques [39]. Advantages are evident in a shorter hospital stay [37–43] and a faster return to work [37,40–42]. Postoperative morbidity and mortality are comparable between the 2 techniques in some studies [39]. Others have shown an advantage for the laparoscopic technique [37,38]. Only some studies describe iatrogenic bile duct injuries during laparoscopic cholecystectomy, with an incidence between 1 case of 200 interventions and 1 case in 500 interventions, twice as high compared with the era of open cholecystectomy [44]. A meta-analysis on laparoscopic cholecystectomy for severe acute cholecystitis with gallbladder empyema or a gangrenous gallbladder did not identify increased postoperative local complications compared with normal acute cholecystitis [45]. However, a 3 times higher conversion rate to open cholecystectomy is seen

in these severe cases. Laparoscopic cholecystectomy can be performed safely as a teaching operation, but a low threshold for conversion is recommended to surgeons to prevent local postoperative complications [46]. The Italian ACTIVE trial (Acute Cholecystitis Trial Invasive vs Endoscopic) currently evaluates laparoscopic versus open cholecystectomy for acute cholecystitis in a multicenter, randomized, double-blinded setting [47]. Based on currently available data, laparoscopic cholecystectomy seems to be as good as or even better than open cholecystectomy and is established as the therapy of choice in acute cholecystitis. However, in technically challenging cases, open cholecystectomy remains the surgical modality of choice in respect to safety and success [48].

SUMMARY

Laparoscopic cholecystectomy is widely established as the standard operation in acute cholecystectomy. Valid data from several prospective studies, including a recent large randomized multicenter trial, are available, demonstrating that early cholecystectomy is associated with less morbidity, a shorter length of hospital stay, and lower total hospital costs compared with delayed cholecystectomy after a conservative treatment period with antibiotics. Early cholecystectomy within 24 hours of hospital admission is the therapy of choice in patients fit for surgery and should be implemented as the standard treatment algorithm for this condition.

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