Laparoscopy and Acute Cholecystitis: The Evidence

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5.1 Introduction

Acute cholecystitis is a relevant healthcare problem. Between 3 and 10 % of all patients with abdominal pain have acute cholecystitis [1].

Cholelithiasis accounts for more than 90 % of causes of acute cholecystitis [2, 3]. About 10–15 % of the adult population of Western countries have gallstones [4–7]. About 700,000 cholecystectomies are performed annually in the USA [8]. In Italy more than 101,000 cholecystectomies have been performed in 2011, 90 % of them laparoscopically [9]. About 10–30 % of cholecystectomies are performed for acute cholecystitis [10].

The laparoscopic approach was initially considered being contraindicated for acute cholecystitis, but it has been adopted later, as experience increased, gradually overtaking open cholecystectomy as the preferred procedure even in an acute setting.

The severity of the disease may range from a mild, self-limited illness to a severe, potentially life-threatening illness.

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Between 50 and 70 % of the cases of acute cholecystitis occur in aged patients [11], and steady increase in life expectancy during the past years will make the problem even more relevant in the future. High prevalence of comorbidities in elderly, as well as increased incidence of complications, sepsis, and severe forms of cholecystitis in this population, often causes a serious surgical emergency.

Several international guidelines addressed the issue of diagnosis and treatment of acute cholecystitis [12–15].

5.1.1 Diagnostic Criteria

Diagnosis of acute cholecystitis relies on a combination of local clinical signs, systemic signs of inflammation, and imaging findings. Very similar sets of criteria, able to achieve almost 100 % specificity, have been suggested in the EAES guidelines of 2006 [16] and the Tokyo Consensus Meeting Guidelines [13]; both can be used in the clinical practice.

The EAES guidelines adopted a scheme validated by a systematic review: (a) acute right upper quadrant tenderness for more than 6 h and ultrasound evidence of acute cholecystitis (the presence of gallstones with a thickened and edematous gallbladder wall, positive Murphy's sign on ultrasound examination, and pericholecystic fluid collections) or (b) acute right upper quadrant tenderness for more than 6 h, an ultrasound image showing the presence of gallstones, and one or more of the following: temperature above 38 °C, leukocytosis, and/or C-reactive protein level greater than 10 mg/L [17].

The Tokyo Consensus Meeting, in 2007, focused on a set of diagnostic criteria that are summarized in Tables 5.1 and 5.2 [18]. The same panel, however, in the 2013 revision of their guidelines, agreed that the proposed criteria were ambiguous and difficult to use, and a definite diagnosis could not be supported in current practice without positive diagnostic imaging studies [13].

The guidelines issued in 2013 included Tc-HIDA scan among the imaging techniques to be taken into consideration and proposed a set of severity assessment criteria that formed the basis for their therapeutic strategy [13].

5.1.2 Indications for Laparoscopy

The safety of laparoscopic cholecystectomy for acute cholecystitis has been shown in several studies. Two randomized trials (LoE2) [19, 20], a population-based outcome research (LoE3) [21], and numerous comparative studies demonstrated that laparoscopic cholecystectomy is associated with faster recovery and shorter hospital stay than open cholecystectomy. The US population-based outcome research showed also lower morbidity and mortality for the 6 years examined [21]. A third randomized controlled study demonstrated that the laparoscopic cholecystectomy caused less surgical trauma and immunosuppression (by measuring serum C-reactive protein and tumor necrosis factor-α (TNF-α) secretion of peripheral blood

Table 5.1 Diagnostic criteria for acute cholecystitis

(A) Local signs of inflammation
1. Murphy's sign, (2) RUQ mass/pain/tenderness
(B) Systemic signs of inflammation
1. Fever, (2) elevated CRP (>3 mg/dl), (3) elevated WBC count
(C) Imaging findings: imaging findings characteristic of acute cholecystitis
Definite diagnosis (Tokyo Guidelines 2007) [18]
1. One item in A and one item in B are positive
2. C confirms the diagnosis when acute cholecystitis is suspected clinically
Definite diagnosis (Tokyo Guidelines 2013) [13]
1. One item in A + one item in B + C
Suspected diagnosis (Tokyo Guidelines 2013) [13]
1. One item in A + one item in B

Modified from Yokoe et al. [13, 18]
Note: acute hepatitis, other acute abdominal diseases, and chronic cholecystitis should be excluded

Table 5.2 Imaging findings of acute cholecystitis

Ultrasonography findings (EL 4)
Sonographic Murphy's sign (tenderness elicited by pressing the gallbladder with the ultrasound probe)
Thickened gallbladder wall (>4 mm; if the patient does not have chronic liver disease and/or ascites or right heart failure)
Enlarged gallbladder (long axis diameter >8 cm, short axis diameter >4 cm)
Incarcerated gallstone, debris echo, pericholecystic fluid collection
Sonolucent layer in the gallbladder wall, striated intramural lucencies, and Doppler signals
Magnetic resonance imaging (MRI) findings (LoE2–4)
Pericholecystic high signal
Enlarged gallbladder
Thickened gallbladder wall
Computed tomography (CT) findings (LoE4)
Thickened gallbladder wall
Pericholecystic fluid collection
Enlarged gallbladder
Linear high-density areas in the pericholecystic fat tissue

From Hirota et al. [18]

mononuclear cells) and also confirmed that it was associated with a shorter hospital stay [22]. This evidence supported the EAES recommendation that laparoscopic cholecystectomy be the treatment of choice for acute cholecystitis (EAES Consensus Conference about laparoscopic approach to acute abdomen [12] and EAES Consensus Conference about laparoscopic cholecystectomy, held in 2013).

It cannot be excluded, of course, that the better outcome of the laparoscopic cholecystectomy be related to the medical staff attitude toward expectation of faster recovery rather than to true physiopathological changes (expectation bias). The trial published by Johansson in 2005 was designed to avoid this bias and included a blind

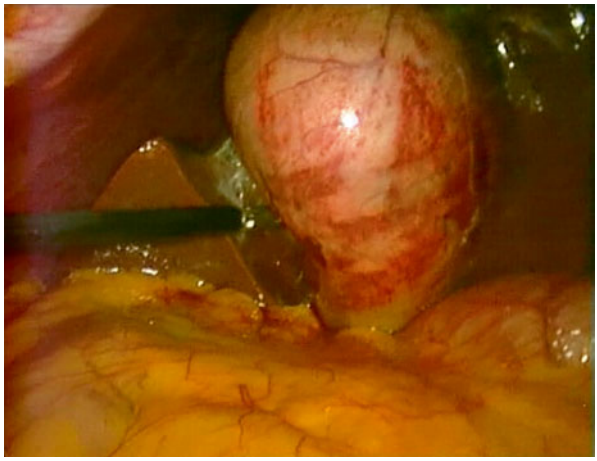

Fig. 5.1 severe cholecystitis: empyema

assessment of outcomes: the wounds were concealed to both patients and postoperative care staff, unaware of the surgical access received by the patient. They showed a very similar postoperative course but still demonstrated a shorter postoperative hospital stay for the laparoscopic group [20].

The preference for laparoscopic cholecystectomy is confirmed by the panel of the Tokyo guidelines, first published in 2007 and recently updated [14], but it is actually limited only to the mildest forms of the disease, excluding most of the severe forms. We will discuss later such a cautious approach and the issue of a therapeutic decision making based on the severity of the local inflammation or the patient general condition as it involves every aspect of the treatment of acute cholecystitis.

Here, it is important to state that review of the literature shows that local inflammatory conditions do not preclude the indication for laparoscopic cholecystectomy (Fig. 5.1). The trial of Kivuloto et al. [19], mentioned above, specifically included gangrenous cholecystitis. Furthermore, a recent review of prospective and retrospective series of severe cholecystitis (gangrenous, empyematous, or perforated) (LoE3) [23] did not show an increase in local postoperative complications and confirmed that laparoscopic cholecystectomy is to be considered an acceptable indication for severe cholecystitis despite a demonstrated threefold conversion rate. The patients examined in the review, and treated by laparoscopic cholecystectomy, would have been instead directed to other treatments by the Tokyo guidelines scheme.

Subtotal cholecystectomy also appears to be an acceptable alternative solution in case of intense inflammation and increased risk of damage to Calot triangle structures (LoE3) [24, 25].

Another subgroup that deserves a separate analysis is the elderly population. The number of elderly with acute cholecystitis has been increasing over the years; earlier reports suggested increased morbidity and higher conversion rate for laparoscopic cholecystectomy in elderly [26]. However, the acute biliary disease appears

to be more severe in the older patients and overall prevalence of comorbidities is higher, making it difficult to extrapolate data from series involving both acute and chronic gallbladder disease [27, 28] or comparing younger versus older patients [29, 30].

Several prospective and retrospective comparative studies examined laparoscopic versus open surgery for acute cholecystitis in elderly patients demonstrating a reduction in the length of hospitalization [31–33] and morbidity either unchanged [31] or improved [32–34] (LoE3).

5.1.3 Timing of Surgery

In the pre-laparoscopic era, randomized controlled trials comparing early versus delayed open cholecystectomy had found that early surgery was associated with a lower complication rate and a briefer hospital stay [35–38]. In the 1990s, however, it was suggested that early treatment of acute cholecystitis by laparoscopic cholecystectomy could be related to an increased risk of conversion and complications, in particular bile duct injury [39]. Since then, the optimal timing of surgical treatment of acute cholecystitis has been extensively debated. A systematic review of the literature found seven randomized controlled trials [40–46] examined in 5 meta-analysis (LoE1) [10, 47–51] comparing early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Six of those seven papers were RCTs (LoE2), but one of the systematic reviews [51] included a nonrandomized study (LoE3) [45].

All the studies agreed that early treatment reduces total hospital stay, without an increase in complication or conversion rates. In particular, rate of bile duct injury seems to be higher in the delayed treated patients, but the difference was not statistically significant due to the small numbers analyzed in the trials [10, 50].

Four further RCTs (LoE2) were not included in any systematic review because they were published later [52–55]. Three of them reported similar results between the two groups; the large trial by Gutt confirmed the superiority of the early cholecystectomy [54].

The definition of time interval for early or delayed surgery, however, varies among the studies: surgery is considered “early” either 4 or 7 days of the onset of symptoms, and planned delay of treatment after index admission may vary between 6 and 12 weeks. In the studies of Chandler [43], the group of delayed treatment included patients operated after resolution of symptoms or within 5 days if the symptoms failed to resolve; those patients would be considered in the “early” group in the rest of the trials; this study has not been included in 3 out of 5 systematic reviews.

The Cochrane review published by Gurusamy and Samraj [50] pointed out that 17.5 % (range 13.9–25 %) of patients included in the delayed surgery groups required urgent surgery during the interval period, for failure of conservative treatment or recurrent symptoms after discharge, and in this subset the conversion rate was 45 %. These data could further support early surgery.

After those studies, several case series were published and confirmed the value of early surgery. However, population-based outcome researches [56–61] showed that practice patterns remain variable worldwide.

Four cost-utility analyses focused on early versus delayed cholecystectomy for acute cholecystitis. Only one of them, performed in a prospective randomized trial, found no significant difference in the cost or outcomes of early laparoscopic cholecystectomy versus delayed treatment, with the latter favored by the incremental cost per additional QALY; however, patients operated on for biliary colic were included in that trial [62]. A model-based economic evaluation and two recent additional analyses found that early surgery is less expensive and results in better quality of life than delayed treatment [63–65].

If the advantages of early laparoscopic cholecystectomy are well defined, the optimal amount of delay for surgery after the onset of symptoms is not completely clarified in the above mentioned studies and deserves a more precise definition. One case series reviewed the issue of the amount of delay between the onset of symptoms and surgery and examined its relation to the conversion rate: the earlier the operation, the lower the risk of conversion. The incidence of conversion is lowest (9.5 %) if surgery is performed within 2 days from the onset of symptoms, rises to 16.1 % if surgery is done within 4 days. After that term, the conversion rate is similar to that of delayed surgery (38.9 %) (LoE4) [66]. However, if one recent observational study confirmed those findings [67], others did not [68–70] (LoE4). A subgroup analysis performed by Gurusamy on the data of his Cochrane review [52] did not show a statistically significant difference between the patients treated less than 4 days from the onset of symptoms and those of the studies including also patients with a longer delay. One large population-based studies, mentioned above, examined the association between outcomes and preoperative length of hospital stay (used as a surrogate marker for the onset of symptoms); their patients were divided into six different groups according to the delay of surgery after hospital admission: group 1, operated on the day of admission; group 2, 1 day after hospital admission; group 3, 2 days; group 4, 3 days; group 5, 4 or 5 days; and group 6, on or after day six. There was no significant association between preoperative length of stay and postoperative mortality or overall morbidity. However, patients hospitalized for two or more days before surgery sustained longer operative times and were significantly more likely to require open cholecystectomy than patients operated on the day of admission. As the time point of surgery is delayed (day of admission versus six and more days after admission), significantly more patients undergo a longer operation and were more likely to be converted to a laparotomy [56]. Similar results were found in the study by Brooks on a total of 5,268 patients [61].

A definitive conclusion on this issue has yet to be reached; however, the available literature allows us to state that cholecystectomy should be performed as early as possible after the onset of symptoms, without evidence of a clear cutoff delay, after which the outcome is significantly worse. Further studies could clarify this issue.

Only one retrospective trial examined the results of early versus delayed treatment in the aged, finding no outcome difference between the two groups [71]. Riall et al., recently, examined a sample of the US Medicare Claims Data System and found

that 75 % of the patients aged 66 years and older, urgently or emergently admitted to an acute care facility for a first episode of acute cholecystitis, received an early cholecystectomy (71 % laparoscopic and 29 % open). The diffuse use of early laparoscopic cholecystectomy in elderly patients confirms that most US surgeons trust that early laparoscopic cholecystectomy should be offered, for acute cholecystitis, even in that age group. The same analysis showed that lack of definitive treatment during initial hospitalization in elderly patients is associated with 38 % gallstone-related readmission rate over the subsequent 2 years (with only 9.5 % of the patients undergoing an elective outpatient cholecystectomy), compared with 4.4 % in patients who underwent early treatment (LoE3) [72].

5.1.4 Percutaneous Cholecystostomy (PC)

Severe comorbidities in elderly or other unstable patients can, however, make early anesthesia or surgery itself too risky. Several alternatives have been proposed for emergency treatment in septic high-risk patients unfit for emergency surgery: conservative treatment (LoE2) [73], tube cholecystostomy followed by early laparoscopic surgery (LoE2) [74] or by delayed surgery (LoE4) [11], and cholecystostomy not followed by surgery (LoE4) [75].

Among the alternatives proposed for the emergency treatment in septic high-risk patients, percutaneous tube cholecystostomy (followed or not by surgery) is extensively reported in the recent literature. In particular the abovementioned Tokyo guidelines consider the percutaneous drainage as mandatory in the severe grade of acute cholecystitis and also suggest its use in the moderate grade, in order to overcome the technical difficulties of an inflamed gallbladder. However, percutaneous gallbladder drainage has never been proven to be an effective alternative to early surgery; the evidence on its role is still lacking.

No randomized controlled trial is yet available on the use of gallbladder drainage in acute cholecystitis. Winbladh et al. published a systematic review with a particularly detailed examination of 53 papers about cholecystostomy as an option in acute cholecystitis (LoE3). The average level of the papers examined in their study is rather poor, and the results are nonhomogeneous. Acknowledged these limitations, the review found no evidence to support the recommendation of percutaneous drainage rather than straight early emergency cholecystectomy even in critically ill patients. Early cholecystectomy actually seems to be a better option for treating acute cholecystitis in the elderly and/or critically ill population [76]. The comparison of the mortality rate after PC (15.4 %) with that after acute cholecystectomy (4.5 %) in similar series shows a significant difference ($p<0.001$) in favor of acute cholecystectomy.

After their review, about 13 retrospective and 2 prospective series have been further published, confirming that the groups considered in the studies, their inclusion criteria, the results, and even the conclusions reached by different authors are largely nonhomogeneous. Bearing in mind these limitations, the reported in-hospital mortality for cholecystostomy varies between 4 and 50 %

(vs. 4.5 % reported for cholecystectomy), and its morbidity ranges between 8.2 and 62 %.

At the present time, percutaneous cholecystostomy cannot be recommended as part of a routine protocol for treatment of acute calculous cholecystitis, but only considered as a possible alternative to reduce anesthesiology risk in a small subset of patients unfit for emergency surgery due to their severe comorbidities. A randomized controlled trial (CHOCOLATE trial) has been planned to attempt to clarify the largely conflicting evidence [77].

5.1.5 Severity Tailored Approach

If the advantages of early laparoscopic cholecystectomy in an unselected population are clarified by the evidence reported above, it can be argued that still it could be possible to improve the overall outcome tailoring the treatment according to the severity of the condition and to the patient status.

The question arises if early surgery, in particular laparoscopic, is indicated for every acute cholecystitis. What is the best treatment for the frailer patients and the more advanced forms of inflammation? Should the clinical decision making take into account a grading system for the severity of the disease and the illness of the patient? As a matter of fact, the heterogeneity of patients, comorbidities, and environment in which this disease presents make the diagnosis, and the subsequent therapeutic procedures, very difficult to standardize; the severity of inflammation and its life-threatening potential are also strongly determined by the general condition of the patient, and the choice of a surgical treatment cannot disregard this aspect [78].

The severity assessment criteria, included in the Tokyo guidelines, take into consideration both general and local factors and classify acute cholecystitis into three severity degrees. An acute cholecystitis is defined “severe” if the condition has developed organ dysfunction and “moderate” if local inflammatory condition (marked leukocytosis, palpable tender mass, onset of symptoms >72 h, gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis) may increase the probability of local complications (“criteria predicting when conditions might be unfavorable for cholecystectomy in the acute phase”). If none of these conditions are present, the cholecystitis is classified as “mild”[13, 18].

Based on that scheme, the Tokyo guidelines recommend early cholecystectomy only in the mild forms (grade I), in which a laparoscopic cholecystectomy is likely to be easy. In the moderate cases, they maintain that medical therapy with or without early gallbladder drainage (surgical or percutaneous) followed by delayed cholecystectomy is indicated, except in “experienced” centers. Cholecystostomy is also preferred for patients placed in the “severe” grade by their organ dysfunction.

Such severity-based classification, however, has not been validated by studies showing an improved outcome after its introduction, and actually a retrospective series failed to find any significant benefit [85].

The severity tailored approach of the Tokyo guidelines ends up in a large use of delayed cholecystectomy, despite the amount of literature against its use. Today, early laparoscopic cholecystectomy is the gold standard, established (as examined above) by evidence level 1 meta-analysis.

Furthermore, several reports show that early cholecystectomy is safe and effective even in the severe forms of the disease (LoE3) [23, 79, 80], (LoE4) [81] or in the elderly population (LoE4) [71, 72, 82].

Finally, a definitive conclusion about the use of percutaneous cholecystostomy has yet to be drawn as discussed above.

Aside from the Tokyo scheme, several clinical scores for the evaluation of surgical risk for acute conditions are available [83], but none is validated for acute cholecystitis. Weighting the risk of early surgery for acute cholecystitis against a well-established risk score could help in identifying those patients with reduced functional reserve who could benefit from a treatment alternative to surgery. The overall outcome of the treatment of this condition could be improved. This selection is not going to be straightforward, until we can achieve a more complete assessment of the results of the alternative treatments available, including morbi-mortality, functional status, and quality of life beyond hospital stay: de Mestral et al., in an elderly population treated by percutaneous cholecystectomy (890 patients among 27, 718 acute cholecystitis between 2004 and 2011), showed that besides a 5 % in-hospital mortality, an additional 18 % of patients had died by 1 year and less than 50 % had received the planned cholecystectomy. An overall 49 % of patients had at least one gallstone-related emergency department evaluation or hospital admission 1 year after discharge [60].

The need for further investigations aimed to a patient-related and evidence-based algorithm that can be related to the clinical and therapeutic decision making for acute cholecystitis remains.

5.1.6 Is Acute Cholecystitis Actually Treated by Laparoscopic Cholecystectomy?

The surgical approach suggested by the Tokyo guidelines appears to be extremely cautious if compared to the findings available in the literature. The EAES Consensus Conference statements are much more assertive in suggesting that laparoscopic cholecystectomy is the treatment of choice for acute cholecystitis and should be performed as soon as possible after the onset of symptoms. Despite the limited surgical indications, the introduction of the Tokyo guidelines seems to be able to increase the adoption of early laparoscopic cholecystectomy as reported by Asai [84].

A Japanese study, based on a large administrative database, examined the records of 6,080 patients with acute cholecystitis from 777 hospitals (68 academic and 709 community hospitals) between April and December of 2008. It is rather surprising to find that only 35 % of those patients received surgery at some point of their hospital course (mean length of stay 20.2 ± 18.2 days). Among the patients who did not receive gallbladder drainage, most likely the mildest forms, only 50.5 % received

early surgery and an additional 13.2 % had cholecystectomy later than 4 days after the hospitalization [58]. After all the introduction of their paper reveals a preconceptual nonsurgical attitude when states that antimicrobial therapy is the mainstay of therapy for acute cholecystitis followed by drainage if the patient fails to improve.

If the Japanese database showed a low cholecystectomy rate for acute gallbladder disease, Western population-based studies reported rates higher but still inferior to the expectations if the indications provided by the literature are to be considered. A report by Csikesz et al., based on the US National Hospital Discharge Survey, demonstrated that the cholecystectomy rate on the first admission was 40 % in the years between 2000 and 2005 [21]. Sandzén et al., on a similar Swedish database, examined between 1988 and 2006, reported that surgery was performed during the index admission in 32.2 % of cases [59]. Only the study on the Medicare Claims Data System, published by Riall et al., reported an overall 75 % cholecystectomy rate during the first admission [72] between 1996 and 2005. It has to be specified that, unlike the Japanese study, the time frame taken into consideration by these reports includes years in which the use of laparoscopy was not widespread.

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