CLINICAL PRACTICE

Acute Calculous Cholecystitis

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A previously well 42-year-old woman presents with severe pain in the right upper quadrant, which started 15 hours earlier. She has previously noted episodic pain in that location that lasted for up to 2 hours but has not sought medical advice. She has had one episode of vomiting with the current attack. On physical examination, her temperature is 38.5°C, and the heart rate is 95 beats per minute. She has tenderness and guarding in the right upper quadrant. How should her condition be evaluated and treated?

THE CLINICAL PROBLEM

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Acute calculous cholecystitis is a complication of cholelithiasis, a condition that afflicts more than 20 million Americans annually[1] and results in direct costs of more than $6.3 billion.[2] Most patients with gallstones are asymptomatic. Of such patients, biliary colic develops in 1 to 4% annually,[3-5] and acute cholecystitis eventually develops in about 20% of these symptomatic patients if they are left untreated.[6] Such patients tend to be somewhat older than those with uncomplicated symptomatic cholelithiasis. Most patients with acute cholecystitis have had attacks of biliary colic, but some have had no previous biliary symptoms.[3-5] After an initial attack of acute cholecystitis, additional attacks of pain or inflammation are common.[7] In a small proportion of patients, acute cholecystitis may coexist with choledocholithiasis, cholangitis, or gallstone pancreatitis.

About 120,000 cholecystectomies are performed for acute cholecystitis annually in the United States. However, the incidence of acute cholecystitis seems to be falling because of the greater acceptance by patients of laparoscopic cholecystectomy as a treatment for symptomatic gallstones.[8] About 60% of patients with acute cholecystitis are women. However, acute cholecystitis develops in men more frequently than would be expected from the relative prevalence of gallstones (about half that in women),[1] and cholecystitis tends to be more severe in men.[9] In patients with diabetes who have symptomatic gallstones, acute cholecystitis seems to develop more frequently than in patients without diabetes, and such patients are more likely to have complications of acute cholecystitis when it occurs.[10]

PATHOGENETIC FEATURES

More than 90% of cases of acute cholecystitis are associated with cholelithiasis (acute calculous cholecystitis). The key elements in pathogenesis seem to be an obstruction of the cystic duct in the presence of bile supersaturated with cholesterol.[11] Brief impaction may cause pain only, but if impaction is prolonged over many hours, inflammation can result. With inflammation, the gallbladder becomes enlarged, tense, and reddened, and wall thickening and an exudate of pericholecystic fluid may develop. The inflammation is initially sterile in most cases, but sec-

ondary infection with microorganisms in the Enterobacteriaceae family or with enterococci or anerobes occurs in the majority of patients.[12,13] The wall of the gallbladder may undergo necrosis and gangrene (gangrenous cholecystitis). Bacterial superinfection with gas-forming organisms may lead to gas in the wall or lumen of the gallbladder (emphysematous cholecystitis). Without appropriate treatment, the gallbladder may perforate, with the development of an abscess in the right upper quadrant or liver or generalized peritonitis.

STRATEGIES AND EVIDENCE

DIAGNOSIS

The main symptom of uncomplicated cholelithiasis is biliary colic, caused by the obstruction of the gallbladder neck by a stone. The pain is characteristically episodic, severe, and located in the epigastrium or right upper quadrant. It frequently follows food intake or comes on at night. Patients commonly have pain that radiates into the back, accompanied by nausea and vomiting. Acute cholecystitis usually begins with an attack of biliary colic, often in a patient who has had previous attacks, but the pain persists and localizes in the right upper quadrant. The bilirubin level may rise to 4 mg per deciliter (68 μmol per liter) in the absence of complications. However, frank jaundice is uncommon; when present, it should raise suspicion of concomitant choledocholithiasis, Mirizzi's syndrome (obstruction of the bile duct as a result of external compression of a stone in the gallbladder or cystic duct), or other complication, such as gallbladder perforation.

Tenderness and guarding in the right upper quadrant are frequent signs. A palpable mass is present in one quarter of patients after 24 hours of symptoms but is rarely present early in the clinical course. Murphy's sign — the arrest of inspiration while palpating the gallbladder during a deep breath — may be useful, particularly when direct tenderness is absent (e.g., in a subsiding case). Occasionally, acute cholecystitis may cause systemic sepsis and organ failure, usually in the setting of gangrenous or emphysematous cholecystitis. Fever and an elevation in the white-cell count are classically described in patients with acute cholecystitis, but either or both may be absent.[14] The C-reactive protein level is frequently elevated.[15] An elevated serum amylase level suggests concomitant gallstone pancreatitis or gangrenous cholecystitis. In elderly patients, delays in diagnosis are common, since the only symptoms may be a change in mental status or decreased food intake, and physical examination and laboratory indexes may be normal.[16,17]

IMAGING

Abdominal ultrasonography and hepatobiliary scintigraphy are the imaging studies most commonly used in diagnosis. Ultrasonography detects cholelithiasis in about 98% of patients (Fig. 1). Acute calculous cholecystitis is diagnosed radiologically by the concomitant presence of thickening of the gallbladder wall (5 mm or greater), pericholecystic fluid, or direct tenderness when the probe is pushed against the gallbladder (ultrasonographic Murphy's sign). In a study involving 497 patients with suspected acute cholecystitis, the positive predictive value of the presence of stones and a positive ultrasonographic Murphy's sign was 92%, and that of stones and thickening of the gallbladder wall was 95%.[18] The negative predictive value of the absence of stones combined with either a normal gallbladder wall or a negative Murphy's sign was 95%.[18]

Hepatobiliary scintigraphy involves intravenous injection of technetium-labeled analogues of iminodiacetic acid, which are excreted into bile. The absence of gallbladder filling within 60 minutes after the administration of tracer indicates obstruction of the cystic duct and has a sensitivity of 80 to 90% for acute cholecystitis (Fig. 2). The false positive rate of 10 to 20% is largely explained by cystic-duct obstruction induced by chronic inflammation, although in some cases normal gallbladders do not fill as a result of insufficient resistance at the sphincter of Oddi. The specificity of the test can be improved by intravenous administration of morphine, which induces spasm of this sphincter.[19] When the cystic duct is patent (i.e., no cholecystitis), the gallbladder is normally visualized within 30 minutes. When gallbladder filling occurs within 30 minutes, the false negative rate (i.e., the presence of cholecystitis despite negative results) is only 0.5%,[20] but filling between 30 minutes and 4 hours is associated with false negative rates of 15 to 20%.[20] The "rim sign" is a blush of increased pericholecystic radioactivity,
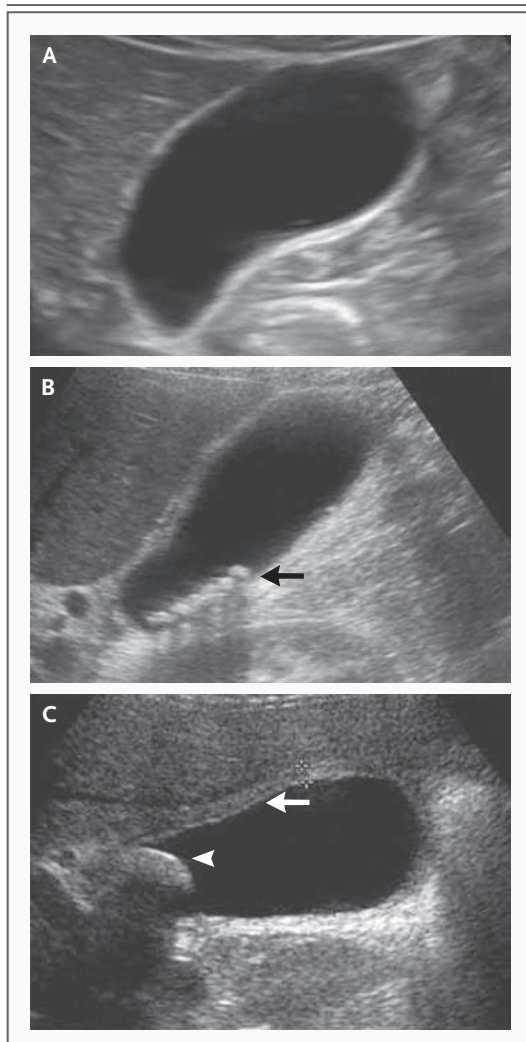
Figure 1. Ultrasonographic Images of Three Gallbladders.

A normal, sonolucent gallbladder (Panel A) is characterized by a thin wall and an absence of acoustic shadows. In a patient with symptomatic gallstones (Panel B), the gallbladder contains small echogenic objects with posterior acoustic shadows that are typical of gallstones (arrow), with a normal wall thickness. In a patient with acute calculous cholecystitis (Panel C), thickening is visible in the gallbladder wall (arrow), along with a large gallstone (arrowhead).

availability, ease, a lack of interference from raised serum bilirubin levels (since cholestasis interferes with biliary excretion of the agents used in scintigraphy), the absence of ionizing radiation, and an ability to provide information regarding the presence of stones. Increasingly, emergency medicine physicians are being trained in the use of ultrasonography.[23] Hepatobiliary scintigraphy is usually reserved for the 20% of patients in whom the diagnosis is unclear after ultrasonography has been performed.

DIAGNOSIS AND GRADING

The gold standard for diagnosis is pathological examination of the gallbladder. There is controversy regarding the optimal criteria for clinical diagnosis. Table 1 summarizes a recently recommended set of diagnostic criteria, called the "Tokyo guidelines."[24,25] Limitations of these criteria are that the condition of patients with few systemic symptoms tends to be underdiagnosed and that testing of the C-reactive protein level is uncommonly used for the diagnosis of acute cholecystitis in the United States. The Tokyo consensus conference also classified the severity of acute cholecystitis with the goal of guiding therapy, particularly cholecystectomy (Table 2).[25] Although no prospective study has determined the breakdown of cases falling into the three categories of the classification, a large majority of cases are mild.

TREATMENT

Timing of Cholecystectomy

Cholecystectomy can be performed by laparotomy or by laparoscopy, either at the time of the initial attack (early treatment) or 2 to 3 months after the initial attack has subsided (delayed treatment). A factor complicating the assessment of outcomes of early treatment is that "early" has been variably defined as anywhere from 24 hours to 7 days after either the onset of symptoms or the time of diagnosis. If delayed, or "conservative," treatment is selected, patients are treated during the acute phase with antibiotics and intravenous fluids and are given nothing by mouth. Narcotics and, in some cases, nonsteroidal anti-inflammatory drugs are used for pain, and occasionally patients undergo percutaneous cholecystostomy (placement of a tube in the gallbladder).

Early laparoscopic cholecystectomy is considered the treatment of choice for most patients. In randomized and prospective trials compar-
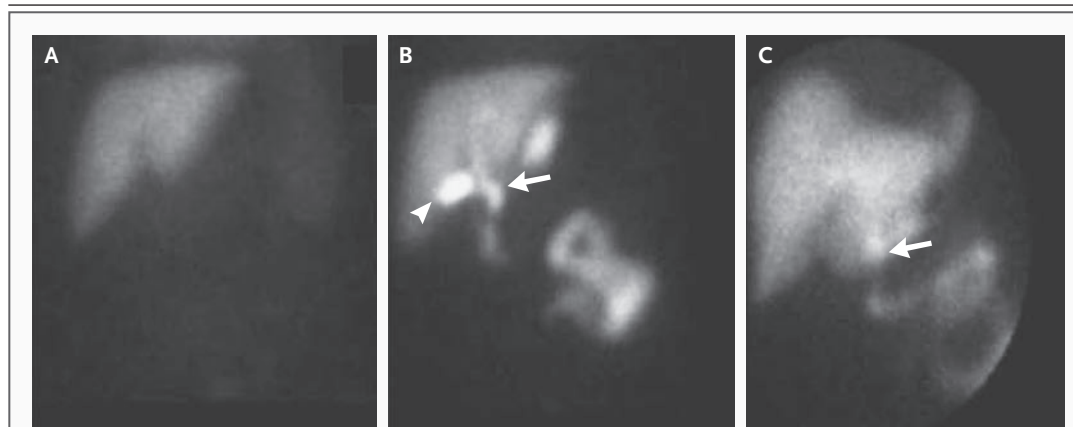
which is present in about 30% of patients with acute cholecystitis and in about 60% with acute gangrenous cholecystitis.

In comparisons of ultrasonography and hepatobiliary scintigraphy in patients with suspected acute cholecystitis, scintigraphy had significantly higher specificity[21] and higher accuracy[22] than ultrasonography. Nonetheless, ultrasonography is usually favored as the first test because of ready

Figure 2. Hepatobiliary Scintigraphy.

In Panel A, a normal liver is visible 10 minutes after the intravenous injection of a technetium-labeled analogue of iminodiacetic acid. In Panel B, at 55 minutes after tracer injection, filling of the bile duct (arrow) and gallbladder (arrowhead) can be seen. In Panel C, at 1 hour after tracer injection in a patient with acute cholecystitis and obstruction of the cystic duct, there is filling of the bile duct (arrow) but no filling of the gallbladder.

ing early laparoscopic cholecystectomy with a delayed procedure,[26-31] as well as in meta-analyses of these trials,[7,32-34] early treatment has consistently been associated with shorter overall hospitalization. Also favoring early cholecystectomy is that approximately 15 to 20% of patients who underwent delayed procedures in the randomized trials had persistent or recurrent symptoms requiring intervention before their planned operation.[7]

The individual trials and meta-analyses have also shown no significant differences between groups in morbidity or mortality or in operative time or conversion rates to open cholecystectomy. However, the relatively small size of the studies (the largest meta-analysis involved only 504 patients) means that an increased risk of uncommon complications — in particular, major bile-duct injury, a complication associated with significant morbidity and, in rare cases, mortality — cannot be convincingly ruled out. For instance, in the Cochrane review, conclusions were drawn from a total of four bile-duct injuries among 438 patients (0.9%).[7] Bile-duct leaks, a form of biliary injury[35] but considered separately, were more frequent in the group undergoing early procedures (3.2%) than in those undergoing delayed procedures (0%).[7] Data from large, population-based studies suggest that biliary injury is more common when the laparoscopic cholecystectomy is performed on an acutely inflamed gallbladder.[36,37] Also of concern is that

small, randomized, controlled trials comparing open cholecystectomy with laparoscopic cholecystectomy did not show an increased risk of biliary injury with laparoscopic cholecystectomy, yet this trend became apparent through analysis of large registries of patients that documented procedural complications. Adequately powered studies are still needed to determine whether the timing of laparoscopic cholecystectomy in acute cholecystitis affects the rate of major bile-duct injuries.

There were no deaths reported in any of the cited randomized trials, but mortality was more than 15% in a recent study of patients with acute cholecystitis who were at high risk (a score of 12 or more on the Acute Physiology and Chronic Health Evaluation [APACHE]).[38] When laparoscopic cholecystectomy is performed in patients with moderately severe acute cholecystitis, it should be done by a highly experienced surgeon. If operative conditions make anatomical identification difficult, the laparoscopic procedure should be converted to an open cholecystectomy or terminated by cholecystostomy.

The rate of conversion to open cholecystectomy is higher when laparoscopic cholecystectomy is performed for acute cholecystitis than for uncomplicated cholelithiasis, and this is true whether the operation is performed in the acute phase[39] or after a delay.[40] Conversion rates range from under 5% to 30%. Predictors of the need for conversion include a white-cell count of more

Table 1. Diagnostic Criteria for Acute Cholecystitis, According to Tokyo Guidelines.*

Clinical manifestations

Local symptoms and signs

    Murphy's sign

    Pain or tenderness in the right upper quadrant

    Mass in the right upper quadrant

Systemic signs

    Fever

    Leukocytosis

    Elevated C-reactive protein level

Imaging findings

    A confirmatory finding on ultrasonography or hepatobiliary scintigraphy

Diagnosis

The presence of one local sign or symptom, one systemic sign, and a confirmatory finding on an imaging test

* Data are from Takada et al.[24] and Hirota et al.[25]

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than 18,000 cells per cubic millimeter at the time of presentation,[41,42] a duration of symptoms of more than a range of 72 to 96 hours,[41,43] and an age over 60 years.[41,44,45]

Antibiotic Therapy

The rationales for the use of antibiotics and the choice of which antibiotic to use are based on the results of bile cultures from patients with acute cholecystitis.[12,13] The guidelines of the Infectious Diseases Society of America recommend that antimicrobial therapy be instituted if infection is suspected on the basis of laboratory and clinical findings (more than 12,500 white cells per cubic millimeter or a temperature of more than 38.5°C) and radiographic findings (e.g., air in the gallbladder or gallbladder wall). Such therapy should include coverage against microorganisms in the Enterobacteriaceae family (e.g., a second-generation cephalosporin or a combination of a quinolone and metronidazole); activity against enterococci is not required.[46] Antibiotics are also recommended for routine use in patients who are elderly or have diabetes or immunodeficiency and for prophylaxis in patients undergoing cholecystectomy to reduce septic complications even when infection is not suspected. In a randomized trial of the use of cefamandole in patients with acute cholecystitis who underwent open cholecystectomy, a short course (three doses) was as effective as a 7-day course.[47] The first dose of an antibiotic should be given within 1 hour before cholecystectomy. It is advisable to culture the gallbladder bile at the time of surgery to guide the selection of antibiotics in the event that postoperative septic complications should arise. The nonsteroidal antiinflammatory drug diclofenac has been shown to reduce pain in patients with biliary colic,[48] but trials are lacking to assess its effects in patients with acute cholecystitis.

Percutaneous Cholecystostomy

Percutaneous cholecystostomy that is performed under local anesthesia with radiologic guidance is often used when the patient presents with sepsis (severe acute cholecystitis, according to the Tokyo guidelines) and in cases in which conservative treatment alone fails, especially in patients who are poor candidates for surgery. Percutaneous cholecystostomy has a high technical success rate and low complication rate and usually results in resolution of acute cholecystitis.[49] However, in a randomized trial in high-risk patients, routine percutaneous cholecystostomy was not superior to conservative measures followed by percutaneous cholecystostomy when needed.[38] Drainage may be followed by delayed cholecystectomy or percutaneous stone extraction in patients who are poor operative candidates. Operative cholecystostomy is used when cholecystectomy cannot be completed because of difficult operative conditions.

GUIDELINES

The Tokyo guidelines provide recommendations for management depending on the severity of acute cholecystitis.[50] For mild acute cholecystitis, early laparoscopic cholecystectomy is recommended. For moderate acute cholecystitis, the guidelines state that either early or delayed cholecystectomy may be selected but that early laparoscopic cholecystectomy should be performed only by a highly experienced surgeon and promptly terminated by conversion to open cholecystostomy if operative conditions make anatomical identification difficult. In the small minority of patients with severe acute cholecystitis, initial conservative management with antibiotics is recommended, preferably in a high-acuity setting, with the use of percutaneous cholecystostomy as needed; surgery is reserved for patients in whom this treatment fails. The guidelines of the Infectious Diseases So-

Table 2. Severity Grading for Acute Cholecystitis, According to Tokyo Guidelines.*

Grade	Criteria
Mild (grade 1)	Acute cholecystitis that does not meet the criteria for a more severe grade Mild gallbladder inflammation, no organ dysfunction
Moderate (grade 2)	The presence of one or more of the following: Elevated white-cell count (>18,000 cells per cubic millimeter) Palpable, tender mass in the right upper quadrant Duration >72 hr Marked local inflammation including biliary peritonitis, pericholecystic abscess, hepatic abscess, gangrenous cholecystitis, emphysematous cholecystitis
Severe (grade 3)	The presence of one or more of the following: Cardiovascular dysfunction (hypotension requiring treatment with dopamine at ≥5 µg per kilogram of body weight per minute or any dose of dobutamine) Neurologic dysfunction (decreased level of consciousness) Respiratory dysfunction (ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen <300) Renal dysfunction (oliguria; creatinine level, >2.0 mg/deciliter) Hepatic dysfunction (prothrombin time–international normalized ratio, >1.5) Hematologic dysfunction (platelet count, <100,000 per cubic millimeter)

* Data are from Hirota et al.[25]

ciety of America for the use of antibiotics in acute cholecystitis are discussed above.[46]

AREAS OF UNCERTAINTY

Most published studies of outcomes of laparoscopic cholecystectomy are from tertiary care centers and involve a relatively small number of patients. Large, population-based studies are required to determine outcomes and rates of complications, particularly rates of biliary injury. Randomized trials of early versus late cholecystectomy with a particular focus on patients with moderately severe acute cholecystitis are also needed. Most general surgeons are very adept at laparoscopic cholecystectomy but are increasingly less experienced at open cholecystectomy, especially in the presence of a high degree of acute or chronic inflammation ("the difficult gallbladder"). It has been recommended that surgeons and centers with less experience in difficult cholecystectomies should perform cholecystostomy when operative difficulty is encountered due to advanced inflammation, followed by referral to a high-volume center for later cholecystectomy,[51] but studies are needed to assess whether this approach reduces the rate of complications. More data are needed to guide the most appropriate use of antibiotics in this condition.

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette has symptoms highly suggestive of acute cholecystitis. She should be hospitalized, given nothing by mouth, and started on intravenous fluids. Abdominal ultrasonography, which is likely to show gallstones and signs of acute cholecystitis such as a thickened gallbladder wall and pericholecystic fluid, should be performed immediately. Since her presentation is consistent with mild (grade 1) acute cholecystitis, prompt laparoscopic cholecystectomy with perioperative antibiotic coverage would be recommended, given the available data suggesting that early laparoscopic cholecystectomy is safe and results in a reduced overall duration of hospitalization.

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