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Acute Cholecystitis: The Diagnostic Role for Current Imaging Tests

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Acute cholecystitis is a relatively common clinical entity characterized histopathologically by obstruction of the cystic duct due to either edema or stone or both. Thorough clinical assessment and selection of the appropriate diagnostic tests are crucial in making an early diagnosis before surgical treatment. Many diagnostic tests are available for imaging the gallbladder. Hepatobiliary imaging using technetium Tc 99m IDA is the test of choice to either exclude or confirm the diagnosis of acute cholecystitis and it carries a discriminating power greater than that of cholecystography or ultrasonography. In most patients the exclusion of the diagnosis of acute cholecystitis can be made as early as 30 minutes and the confirmation within three hours. The confirmation of acute cholecystitis by radionuclide imaging obviates the need for either cholecystography or ultrasonography.

GALLBLADDER DISEASE is considered one of the nation's major medical problems.[1] Annually 500,000 cholecystectomies are done in the United States for either acute or chronic cholecystitis. Acute cholecystitis (AC) usually presents as an emergency in terms of both diagnostic urgency and therapeutic intervention and of course any delay in diagnosis further delays therapy. Immediate cholecystectomy is recommended as the proper therapy for acute cholecystitis on the basis that there is no evidence of increased operative mortality or morbidity associated with early cholecystectomy.[2-6] A recent *Lancet* editorial stated that "once the diagnosis has been confirmed the patient should be put on the next convenient operating list for cholecystectomy under antibiotic cover."[7] Such a measure is thought to reduce up to ten days the hospital stay for each patient, in contrast to conservative (late) cholecystectomy.[8,9] With these recent changing trends in management, attention has shifted toward the need for early diagnosis.

Clinical Assessment

A thorough clinical assessment and a high index of suspicion of AC are essential in any patient who presents with acute right upper quadrant pain and fever. Other clinical conditions that mimic AC include appendicitis, gastritis, pancreatitis, acute myocardial infarction, right lower lobe pneumonia and right renal colic. Fever, right upper quadrant pain and a positive Murphy's sign are well-established signs and symptoms of acute cholecystitis. In one study when the clinical prob-

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ABBREVIATION USED IN TEXT

AC=acute cholecystitis

ability was less than 50 percent, none of the patients with right upper quadrant pain and fever had AC. When the probability was between 51 percent and 99 percent, 16 of 33 patients (49 percent) had AC; and when the probability was between 90 percent and 99 percent, 10 of 13 patients (77 percent) had AC (Table 1). As 23 percent of patients with the highest clinical probability did not have AC, it is evident that a complete clinical examination alone cannot be relied on as the final indication for a surgical procedure.[10] Due to such a high false-positive fraction, it is necessary to confirm AC via other, primarily imaging, diagnostic tests.

The available imaging tests for detecting AC and their current costs (in Portland) are shown in Table 2. The results of most tests are usually evaluated in terms of sensitivity (also called true-positive ratio, which indicates the fraction of times the test findings are abnormal or positive in patients with AC) and specificity (also called true-negative ratio, which indicates the fraction of times the test findings are negative or normal in a group of persons without AC). As none of the imaging tests are perfect and sensitivity deals only with the ill population and specificity deals only with the well population, they do not enlighten on the more important question: What is the likelihood of AC being present when a test result is either positive (abnormal) or negative (normal)? To answer these questions, one has to take into account, in addition, the prevalence of the disease in the population under study and the false-negative (fraction of times the test results are normal in patients with AC) and false-positive (fraction of times the test results are abnormal in subjects without AC). Using these additional parameters, one can evaluate the true meaning of the test result in terms of likelihood of disease.

Imaging Techniques

Seven different types of noninvasive imaging tests are available for the detection of AC (Table 2). Depending on a physician's confidence and familiarity, he or she may decide to choose all of them or, more likely, a combination of a few. A plain x-ray film of the abdomen occasionally will show gallstones or a calcified gallbladder wall or ileus. Plain x-ray films do not show AC directly but are used primarily to detect changes accompanying AC.[11-13]

Cholecystography (Oral)

Since its introduction in 1924, cholecystography using contrast media given orally has been the standard diagnostic test for detecting gallbladder disease.[14] For the gallbladder to be visualized on

TABLE 1.—*Accuracy of Clinical Assessment in the Diagnosis of Acute Cholecystitis (AC)**

Clinical Probability of AC: Percent	(No. of patients)	No Acute Cholecystitis: Number	(percent)	Acute Cholecystitis: Number	(percent)
10-49	(3)	3	(100)	..	..
50-99	(33)	17	(51)	16	(49)
90-99	(13)	3	(23)	10	(77)
10-99	(36)	20	(55)	16	(45)

*Reproduced with permission from Freitas et al.[10]

TABLE 2.—*Cost in Portland, Oregon, of Noninvasive Diagnostic Imaging Tests for Acute Cholecystitis*

Radiographic procedures	
Plain film of abdomen	$ 34
Cholecystography (oral)	73
Cholangiography (intravenous)	112
Tomography (infusion)	96
Computerized tomography of liver and gallbladder	397
Ultrasonography	122
Imaging using radionuclides technetium Tc 99m IDA	265
TOTAL	$1,099
Hospital bed cost per day	$ 195

TABLE 3.—*True-Positive, True-Negative, False-Positive and False-Negative Ratios of Imaging Tests for Acute Cholecystitis*

Test	True-positive (sensitivity) Percent	False-negative Percent	True-negative (specificity) Percent	False-positive Percent
Radionuclide imaging using technetium Tc 99m IDA[18,19,58,59]	95	5	94	6
Cholecystography (oral)[18-20]	75	25	82	18
Ultrasonography[18,46]	50	50	62	38

TABLE 4.—*Total Cost for Confirmation of the Diagnosis of Acute Cholecystitis in Portland, When Only Two Imaging Tests Are Used*

Plain x-ray film of abdomen	$ 34
Technetium Tc 99m IDA imaging	265
TOTAL	$299

the x-ray film, the bile should achieve iodine concentration of 0.25 to 1.0 grams per dl, which occurs between 14 and 19 hours after oral ingestion of the dye.[15-17] The average sensitivity and specificity of a cholecystogram in the diagnosis of AC are 75 percent and 82 percent, respectively (Table 3).[18-20]

Cholangiography using intravenous injection of contrast media depends very much on the functional integrity of the liver cells. The test is of value when the serum bilirubin level is normal and not reliable when the level exceeds 2 mg per dl.[21-27] Tomography following infusion of contrast media is based on the fact that an inflamed gallbladder wall in AC is thickened and concentrates the contrast media.[28-31] However, increased wall thickness has also been reported in patients without biliary disease.[32] The role of computerized tomography is not clearly established.[33-35]

Ultrasonography

Ultrasonography has been used in the past ten years with increasing frequency.[36-38] The reported accuracy of ultrasound studies for detecting gallstones ranges from 91 percent to 98 percent.[39,40] The echogenic features of all gallstones are similar; hence, ultrasonography cannot reliably differentiate stones in AC from those in chronic cystitis or "silent" (asymptomatic) gallstones. Gallbladder wall thickening is sometimes used as evidence for AC.[23,41-45] However, wall thickening is not specific for AC and is found in patients with hypoalbuminemia, ascites, 10 percent to 45 percent of patients with chronic cholecystitis or partially or completely contracted normal gallbladders[45-50] and in only about 45 percent of patients with AC.[46] When used in conjunction with imaging using radionuclides and with cholecystography on the same group of patients, the sensitivity and specificity of ultrasonography in the detection of AC are shown to be 50 percent and 62 percent, respectively.[18]

Radionuclide Biliary Imaging With Technetium Tc 99m IDA

There are now more than half a dozen agents available for radionuclide hepatobiliary imaging.[51-53] Structurally all are closely related to lidocaine and do not cause any physiologic changes on injection.[54] Because all of the agents work when the serum bilirubin level is normal, whereas only a few are useful at higher bilirubin levels, the selection of an individual agent should be based on the knowledge of serum bilirubin level.[55] Technetium Tc 99m paraisopropyl and parabutyl analogues are more resistant to displacement by bilirubin than dimethyl IDA.[56] The resistance is attributed to their greater protein-binding capacity, which reduces urinary and enhances hepatic excretion.[57]

In normal persons and in patients with normal serum bilirubin levels, the entire biliary system is usually visualized within an hour (Figure 1). In 48 normal volunteers studied in our department, the gallbladder was clearly seen, thus establishing

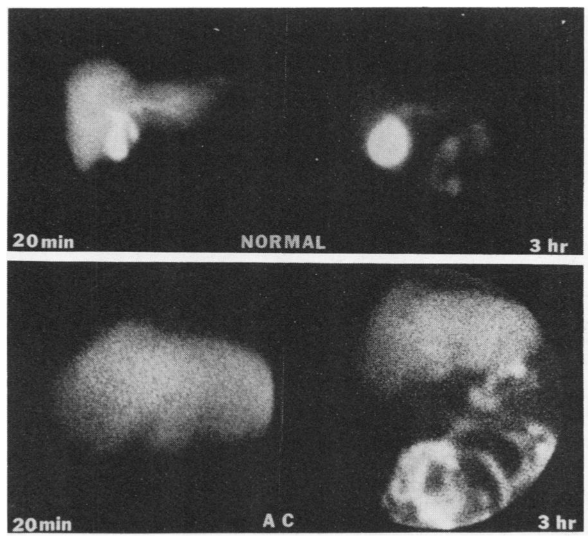

Figure 1.—Technetium TC 99m IDA biliary imaging study in a normal person and in a patient with acute cholecystitis (AC). Note gallbladder appearance at 20 minutes in the normal person and the nonappearance after three hours in the patient with AC.

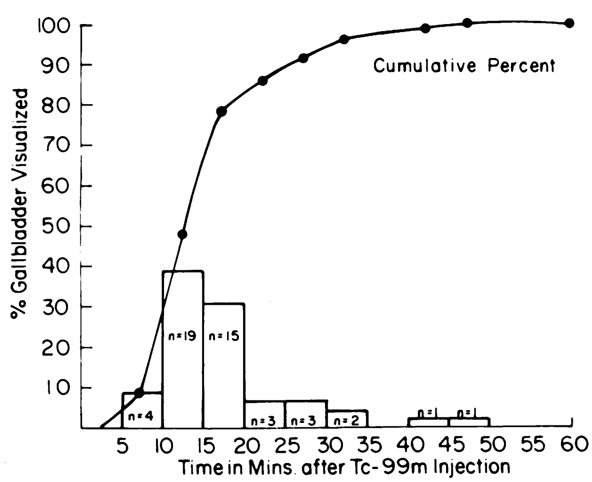

Figure 2.—The time (X axis) of appearance of the gallbladders (Y axis) in 48 normal volunteers following intravenous injection of technetium TC 99m IDA. The number of subjects at each interval is shown inside the column.

the patency of the cystic duct, in 50 percent of the subjects within 15 minutes, 80 percent within 20 minutes and 100 percent within 50 minutes (Figure 2). AC is diagnosed when the gallbladder is not seen (Figure 1). When the gallbladder is seen, the diagnosis of acute cholecystitis can be excluded within 20 minutes; however, the confirmation of the diagnosis requires imaging up to three to four hours. In some patients with chronic cholecystitis or cholelithiasis, or both, the gallbladder is often visualized after three to four hours. The average sensitivity and specificity of radionuclide imaging for AC (Table 3) are 95 percent and 94 percent, respectively.[18,58,59] Eight cases of false-negative hepatobiliary imaging studies with technetium Tc 99m IDA have been reported.[60,61]

Bayes' Analysis

The knowledge of sensitivity, specificity and false-negative and false-positive ratios is essential to compare the relative merits of the diagnostic methods. The optimum choice of sensitivity and specificity should ideally be drawn from analysis of the receiver operating characteristics (ROC) curve.[61] Because no single test can absolutely exclude or confirm AC, the final answer requires the application of bayesian analysis.[61,62] The probability of acute cholecystitis being present when the test result is positive or negative is determined by applying the following formula:

$$\text{probability of AC when test is positive (abnormal)} = \frac{(\text{sensitivity}) \times \text{prevalence of AC in study population}}{\text{sensitivity} \times \text{prevalence of AC in study population} + \text{false-positive fraction} \times \text{prevalence of no AC in study population}}$$

$$\text{probability of AC when test is negative (normal)} = \frac{\text{false-negative fraction} \times \text{prevalence of AC in study population}}{\text{false-negative fraction} \times \text{prevalence of AC in study population} + \text{specificity} \times \text{prevalence of no AC in study population}}$$

The probabilities of AC being present when the test result is either positive (abnormal) or negative (normal) are shown in Figures 3 to 5. The difference in posttest probability between the positive and negative test results is here called the discriminative power of the test. The wider the

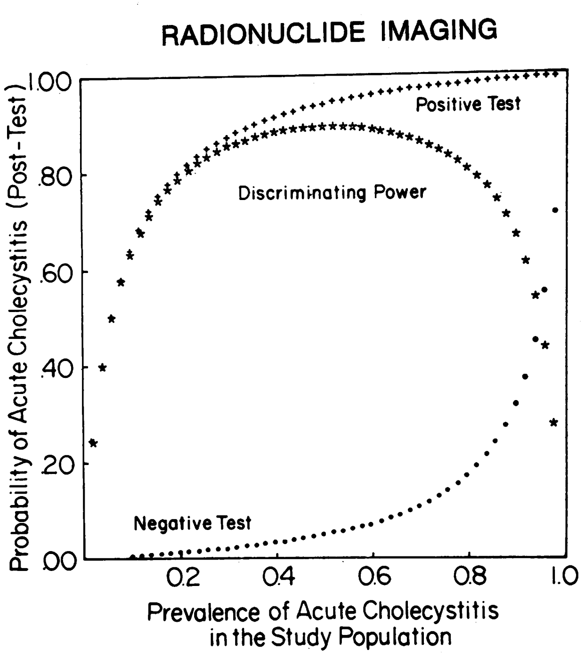

Figure 3.—Radionuclide imaging using technetium Tc 99m IDA. The posttest probability of acute cholecystitis when the test result is either positive (+) or negative (•) is shown on the Y axis and the hypothetical pretest prevalence of acute cholecystitis in the study population is shown on the X axis. Note that a wide difference between positive and negative results in a high discriminating power of the test, with a broad curve between the pretest prevalence rate of 20 percent and 80 percent.

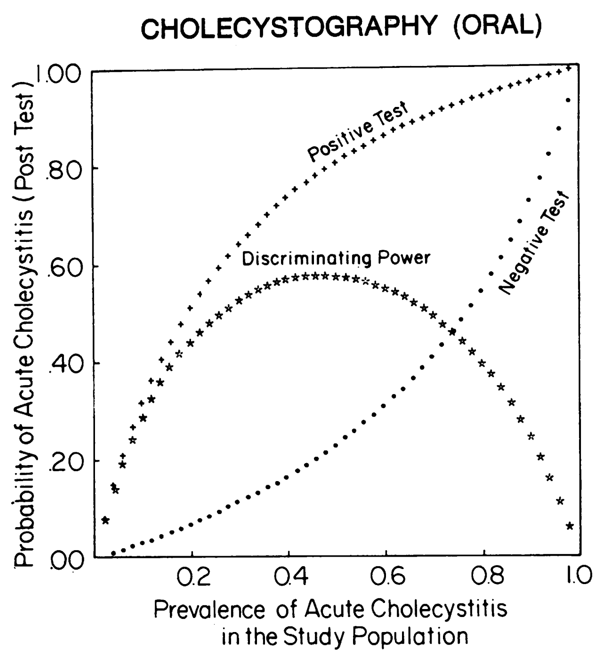

Figure 4.—Cholecystography (oral). The posttest probability of acute cholecystitis when the test result is either positive (+) or negative (•) is shown on the Y axis and the hypothetical pretest prevalence of acute cholecystitis (*) in the study population on the X axis. Note that the difference between positive and negative test results is widest at the pretest prevalence rate of 50 percent and the discriminating power of the test decreases above and below this rate.

difference between the positive and negative result, the greater is the discriminating power. A positive finding is considered to confirm and negative finding to exclude AC.

Relative Merits of Gallbladder Imaging Tests

The prevalence of AC in the study population is variable and depends on age, sex, race, parity, nutrition, geography and other factors.[63] Assume that in the Veterans Administration (VA) population, where most subjects are male, the prevalence of AC is 10 percent of all patients with acute right upper quadrant pain and fever of less than three days' duration. The pretesting probability of AC will be 10 percent. After a thorough clinical examination, a primary physician estimates the clinical probability of acute cholecystitis to be greater than 50 percent and orders a cholecystogram, ultrasound and radionuclide imaging studies without knowing the results of any of the tests. A physician does not request these tests first when the probability of AC is felt to be less than 50 percent.

When the finding of the radionuclide imaging test is positive (that is, the gallbladder is not seen), the probability of AC increases from 10 percent to 63 percent; and when the test finding is negative (gallbladder seen), the probability decreases from 10 percent to 0.5 percent (Figure 3). Here both positive and negative test results are of value. A positive finding on cholecystography increases the pretest probability from 10 percent to 32 percent and a negative test finding decreases the probability from 10 percent to 3.2 percent (Figure 4), so that both positive and negative test results are of some value. A positive result on an ultrasound study (Figure 5) increases the probability from 10 percent to 12 percent and a negative test finding decreases the probability from 10 percent to 8 percent. So here the positive and negative test results are of little value.

A slightly higher prevalence of AC in the study population may be seen in a county, university or private hospital, where about half of the hospital population are women. Assume that the prevalence of AC in middle-aged obese women with right upper quadrant pain and fever of less than three days' duration is 50 percent. A positive radionuclide imaging study then increases the probability from 50 percent before testing to 95 percent posttesting and a negative test result decreases the probability from 50 percent to 5 percent (Figure 3). Once again both positive and negative test results are of considerable value. A positive finding on a cholecystogram in which a contrast medium is given orally increases the probability from 50 percent to 85 percent and a negative finding decreases the probability from 50 percent to 23 percent (Figure 4). A positive result on ultrasonography, however, increases the probability from 50 percent to 56 percent and a negative result decreases the probability from 50 percent to 45 percent (Figure 5).

A still higher prevalence of 80 percent of AC may be found in an urban or rural health clinic serving mainly American Indians, who have one of the highest recorded incidences of gallbladder disease.[63-66] A positive finding on a radionuclide imaging study increases the probability from 80 percent to 98 percent and a negative finding decreases the probability from 80 percent to 17 percent (Figure 3). A positive result on a cholecystogram increases the probability from 80 percent to 94 percent and a negative result decreases the probability from 80 percent to 57 percent (Figure 4). A positive result on ultrasonography increases the probability from 80 percent to 95 percent and a negative result decreases the prob-

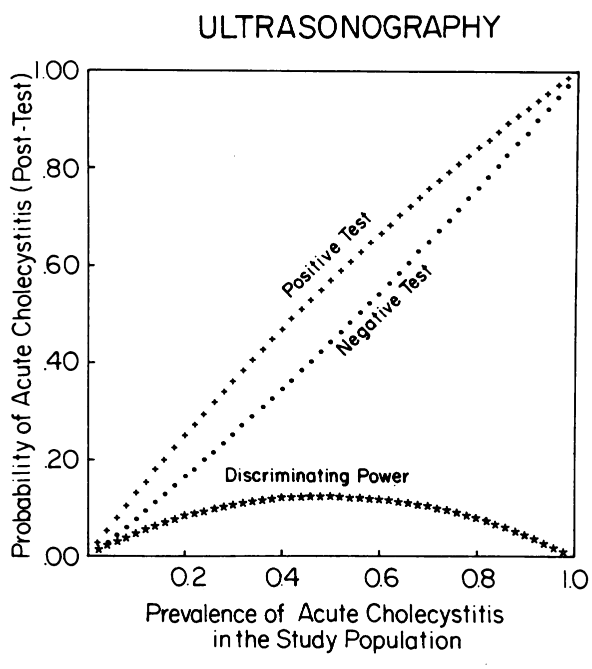

Figure 5.—Ultrasonography. The posttest probability of acute cholecystitis when the test result is either positive (+) or negative (•) is shown on the Y axis and the hypothetical pretest prevalence of acute cholecystitis in the study population (*) on the X axis. Note that both positive and negative result lines run parallel to each other with a narrow separation between them, resulting in a low discriminative power of the test.

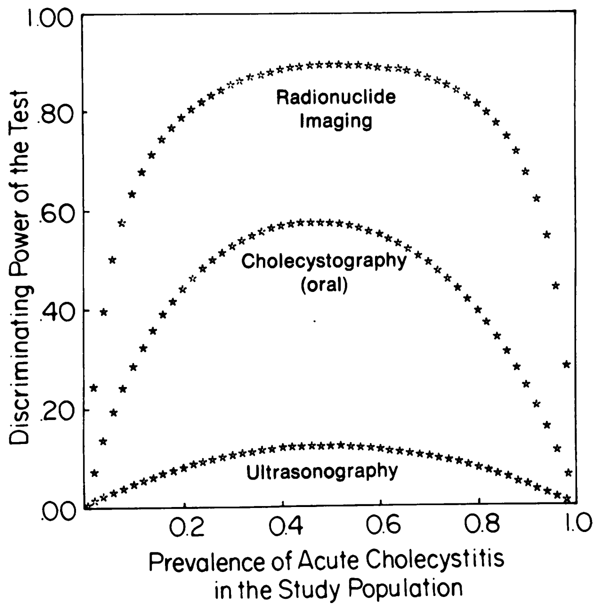

Figure 6.—A comparison of the discriminating power of all three tests in the diagnosis of acute cholecystitis. The hypothetical pretesting prevalence of acute cholecystitis is shown on the X axis. The Y axis shows the power of the test. The value of 1.0 indicates the perfect test.

ability from 80 percent to 75 percent (Figure 5). When the prevalence of AC in the study population exceeds 90 percent, then negative results on any of the tests are not reliable.

The discriminating power of a radionuclide imaging test using technetium Tc 99m is high, with a broad curve for prevalence between 20 percent and 80 percent (Figure 6). Cholecystography (oral) and ultrasonography reach their peak discriminating power at a prevalence rate of 50 percent and have a narrow curve. At a lower prevalence (below 20 percent), radionuclide imaging study shows a rapid rise in discriminating power and superimposes the line for a positive test result. The discriminating line for ultrasonography is almost flat throughout and the line for cholecystography lies between ultrasound study and radionuclide imaging (Figure 6). The discriminating power line descends rapidly downward when the prevalence of AC exceeds 90 percent in the study population.

Comments

As the salient histopathologic feature of AC is cystic duct obstruction,[67] the tests that establish the patency of the cystic duct are most reliable.[68] The exclusion of AC by radionuclide imaging (technetium Tc 99m) can be made in most patients within 30 minutes. Once the diagnosis has been excluded, a physician can then focus attention on an alternative diagnostic workup. Confirmation of the diagnosis of AC, however, requires imaging up to three to four hours. The surgical therapy for AC can thus be instituted within three to four hours after it is first clinically suspected.

About 20 percent of normal gallbladders are not visualized with a single dose of the contrast medium; a double-dose study at 48 hours is required to confirm the diagnosis of AC by cholecystography.[16,17,69] Because almost all patients with AC will have obstruction of the cystic duct and hence nonvisualization of the gallbladder, a cholecystography invariably requires a double dose of the orally given contrast medium. Obviously, this prolongs a hospital stay and delays definitive therapy for as long as two days. An alternative diagnostic workup would also be delayed for 48 hours. In Portland, the average cost of one day in hospital on a general surgical ward is $195. A two-day delay in diagnosis would increase the cost of management of acute cholecystitis by $390 per patient.

In the United States 15 to 20 million people are known to have gallstones. Every year a million new cases are discovered and only half of them are symptomatic, requiring cholecystectomy.[70] Therefore, there is great medical, surgical and socioeconomic risk in equating cholelithiasis with acute cholecystitis. If the total cost of a single cholecystectomy procedure is $3,000, then the annual cost of half a million cholecystectomies in the United States is 1.5 billion dollars. This amount is doubled by simply equating cholelithiasis with acute cholecystitis and treating likewise. Physicians therefore must make a real attempt to distinguish acute cholecystitis from asymptomatic cholelithiasis before submitting a patient to a surgical procedure. The management of AC consists of immediate surgical treatment, whereas chronic cholecystitis is treated by elective surgical procedure.[7]

Before introduction of ultrasonography, symptomatic cholelithiasis was detected by cholecystography. Most of the silent stones were found at autopsy and few by a surgeon while doing an abdominal surgical procedure for some other illness. Many surgeons feel that there is no good reason for treating patients with silent stones. With the ever-increasing frequency of application of abdominal ultrasonography, almost all of silent gallstones can be discovered in vivo.[39] The lesser discriminatory power of ultrasonography in AC is primarily due to the fact that 50 percent of gallstones are silent and that about 10 percent of cases of AC occur in the absence of cholelithiasis.[71-74] Ultrasonography does not establish the patency of the cystic duct, the salient histopathologic feature of AC.

One recent study used the shape (oval or round) and size (diameter greater than 5 cm) as minor criteria for AC.[75] However, this study did not include normal persons to establish the normal range of shape and size. A normal gallbladder has many shapes to it and may become enlarged after prolonged fasting.[76] Recently another study claimed a high degree of ultrasonographic accuracy (86 percent) in the detection of AC. This level of accuracy was achieved primarily because the authors used local tenderness over the gallbladder region (Murphy's sign) as an ultrasonographic sign for AC.[77] This is a very expensive method of eliciting Murphy's sign, which can be substituted at no additional cost to a patient by careful manual palpation by a physician. Interestingly, the same study showed that the presence of stones did not aid in differentiating acute from chronic cholecystitis. Ideally the parameters used to make a diagnosis by an imaging study should be able to be recorded in an image; otherwise, there would be no need for such a study. Local tenderness obviously cannot be imaged and hence should not be used as evidence of acute cholecystitis. It should be pointed out, however, that ultrasonography is a very important tool in the diagnosis of many abdominal diseases and its role should not be underestimated.[36,37] It is the next logical step once the diagnosis of AC is excluded.

The cost of individual imaging tests that are available for the detection of AC is shown in Table 2. Potentially one could use all of the available diagnostic tests for acute cholecystitis and come up with a bill of $1,099. The analysis used here shows that a physician could reduce the cost by restricting the diagnostic workup to include a plain x-ray film of the abdomen and a radionuclide imaging study and thus reduce the cost from $1,099 to $299 (Table 4). A plain x-ray film of the abdomen is retained because of its other useful intra-abdominal information in general.[12]

Many physicians feel that more tests are ordered than are really required for proper clinical management.[78-81] Years ago it was all right to order cholecystography or cholangiography to diagnose AC. Now with recent advances in hepatobiliary imaging, the question has to be asked whether cholecystography, cholangiography and ultrasonography are really needed in 1982 and beyond to confirm a diagnosis of AC. A decision has to be made here whether or not the number of tests required to confirm AC can be reduced. A delay in this decision will result in multiplication of tests[82-84] and increase in cost of medical care. Recent results have shown that a patient with no contraindication for operation and a positive finding on radionuclide imaging test can be subjected to cholecystectomy for AC without any need for additional testing.[85]

Caution should be exercised in doing an imaging test using technetium Tc 99m IDA. As has been shown in normal subjects,[86] preemptying of the gallbladder with cholecystokinin or a fatty meal is probably an undesirable patient preparation that may result in a high false-positive rate, especially in patients with alcoholism or on total parenteral nutrition.[87] Bayesian analysis is more valid, for instance, when the test carries a constant degree of high precision (sensitivity). The hazards of application of bayesian analysis to tests that show variable sensitivity have been elegantly described in a recent report[88] and should be kept in mind by all clinicians.

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