Does This Patient Have Acute Cholecystitis?

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CLINICAL SCENARIO

A 72-year-old woman with a history of poorly controlled diabetes, coronary artery disease, and hypertension presents to the emergency department complaining of nausea and vomiting. As an emergency department resident, you elicit the history that the patient felt well until 24 hours ago, when she developed anorexia followed rapidly by bilious emesis. She describes mild upper abdominal discomfort but is unable to further localize the pain and reports no abnormal bowel movements, gastrointestinal bleeding, or chest pain.

The patient is febrile (39°C) and appears uncomfortable. Her lungs are clear and cardiac examination reveals only a fourth heart sound. There is moderate epigastric tenderness and guarding throughout the abdomen but no rigidity. Pelvic and rectal examination results are unremarkable. Electrocardiography shows no changes suggestive of ischemia. Laboratory testing shows a leukocytosis of $17 500 \times 10^3/\mu L$, serum transaminase levels twice the upper limit of normal, and a total bilirubin level of 3.2 mg/dL (54.7 μmol/L). In considering the differential diagnosis for the patient's presenting complaint and laboratory results, you wonder whether the suspicion of acute cholecystitis is high enough to warrant further testing.

See also Patient Page.

Context Although few patients with acute abdominal pain will prove to have cholecystitis, ruling in or ruling out acute cholecystitis consumes substantial diagnostic resources.

Objective To determine if aspects of the history and physical examination or basic laboratory testing clearly identify patients who require diagnostic imaging tests to rule in or rule out the diagnosis of acute cholecystitis.

Data Sources Electronic search of the Science Citation Index, Cochrane Library, and English-language articles from January 1966 through November 2000 indexed in MEDLINE. We also hand-searched Index Medicus for 1950-1965, and scanned references in identified articles and bibliographies of prominent textbooks of physical examination, surgery, and gastroenterology. To identify relevant articles appearing since the comprehensive search, we repeated the MEDLINE search in July 2002.

Study Selection Included studies evaluated the role of the history, physical examination, and/or laboratory tests in adults with abdominal pain or suspected acute cholecystitis. Studies had to report data from a control group found not to have acute cholecystitis. Acceptable definitions of cholecystitis included surgery, pathologic examination, hepatic iminodiacetic acid scan or right upper quadrant ultrasound, or clinical course consistent with acute cholecystitis and no evidence for an alternate diagnosis. Studies of acalculous cholecystitis were included. Seventeen of 195 identified studies met the inclusion criteria.

Data Extraction Two authors independently abstracted data from the 17 included studies. Disagreements were resolved by discussion and consensus with a third author.

Data Synthesis No clinical or laboratory finding had a sufficiently high positive likelihood ratio (LR) or low negative LR to rule in or rule out the diagnosis of acute cholecystitis. Possible exceptions were the Murphy sign (positive LR, 2.8; 95% CI, 0.8-8.6) and right upper quadrant tenderness (negative LR, 0.4; 95% CI, 0.2-1.1), though the 95% CIs for both included 1.0. Available data on diagnostic confirmation rates at laparotomy and test characteristics of relevant radiological investigations suggest that the diagnostic impression of acute cholecystitis has a positive LR of 25 to 30. Unfortunately, the available literature does not identify the specific combinations of clinical and laboratory findings that presumably account for this diagnostic success.

Conclusions No single clinical finding or laboratory test carries sufficient weight to establish or exclude cholecystitis without further testing (eg, right upper quadrant ultrasound). Combinations of certain symptoms, signs, and laboratory results likely have more useful LRs, and presumably inform the diagnostic impressions of experienced clinicians. Pending further research characterizing the pretest probabilities associated with different clinical presentations, the evaluation of patients with abdominal pain suggestive of cholecystitis will continue to rely heavily on the clinical gestalt and diagnostic imaging.
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Why Is This Question Important?

Acute cholecystitis accounts for 3% to 9% of hospital admissions for acute abdominal pain.[1-4] The majority of patients presenting with upper abdominal complaints are subsequently found to have a relatively benign cause of pain (eg, dys-

pepsia or gastroenteritis),[2,5] but the possibility of acute cholecystitis mandates the completion of a comprehensive and at times laborious diagnostic evaluation. The importance of this clinical dilemma is only magnified by the frequency with which abdominal pain is encountered in clinical practice.[6-8]

Traditionally, the diagnosis of acute cholecystitis was followed by a several-week "cooling off" period before proceeding to surgery. Most clinicians now advocate early cholecystectomy (ie, within several days of the onset of symptoms),[9] on the basis of lower complication rates, reduced costs, and shortened recovery periods.[10-14] These findings suggest that delayed or missed diagnosis increases morbidity, though this impact has not been specifically addressed.

Definition of Cholecystitis

Defining cholecystitis as "inflammation of the gallbladder" implies a pathologic state. What clinicians usually mean by acute cholecystitis, however, is the presence of this pathologic state (seen macroscopically at laparotomy or microscopically by the pathologist) in the setting of a plausibly related clinical presentation. Practically speaking, cholecystitis is a syndrome encompassing a continuum of clinicopathologic states. At one end of this continuum is symptomatic cholelithiasis, with acute attacks of pain (biliary colic) that resolve in 4 to 6 hours. At the other end, that which is typically associated with the term "acute cholecystitis," is a clinical picture in which biliary colic is longer lasting and accompanied by fever, laboratory markers of inflammation, or cholestasis.[15,16] Gallbladder inflammation without gallstones (ie, acalculous cholecystitis) typically occurs in critically ill patients and is consequently associated with a high mortality rate.[17,18]

How to Elicit the Relevant Signs and Symptoms

Cope's Early Diagnosis of the Acute Abdomen[15] points out that "biliary colic" is a misnomer, since biliary obstruction produces pain of a steady, nonparoxysmal nature. A majority of studies have explicitly defined biliary colic in similar terms (eg, a steady right upper quadrant pain lasting for at least 30 minutes), but others have used the term without definition.[19] *Cope's* also stresses that biliary colic localizes to the mid epigastrium as often as to the right upper quadrant. A recent systematic review[19] supports this observation, as "upper abdominal pain" exhibited test characteristics comparable to right upper quadrant pain. Thus, the clinician should inquire about both pain in the upper quadrant and more generally pain in the upper abdomen. The clinician should also ask the patient about fat intolerance, as abdominal discomfort following fatty meals may have a predictive value similar to that of biliary colic.[19]

Physical findings most famously associated with the gallbladder are the Courvoisier and Murphy signs. The Courvoisier sign has evolved in meaning,[20] but standard definitions describe the sign as referring to a palpable, nontender gallbladder in a patient with jaundice.[21,22] Courvoisier observed that dilation of the gallbladder occurred more commonly when obstruction resulted from malignancy, rather than from benign conditions such as gallstones. While this association is real, the sign should not be elevated to the status of a "law,"[20-22] as recent reports confirm the occurrence of the Courvoisier sign in biliary conditions other than obstructive malignancies.[23]

The Murphy sign refers to pain and arrested inspiration occurring when an examiner's fingers are hooked underneath the right costal margin during deep inspiration.[21,22,24] Data addressing the usefulness of the Murphy sign in evaluating patients suspected of having acute cholecystitis are discussed along with other findings from the systematic review presented below. The only other physical sign we identified as specifically associated with acute cholecystitis was the Boas sign. Originally this sign referred to point tenderness in the region to the right of the 10th to 12th thoracic vertebrae,[25-27] but contemporary sources describe hyperesthesia to light touch in the right upper quadrant or infrascapu-lar area.[22] One study[28] reported that 7% of patients undergoing cholecystectomy exhibited hyperesthesia in this region, but no patient exhibited the Boas sign in the original sense. None of the other studies reviewed below assessed the Boas sign in either form.

Accuracy of Diagnostic Imaging

Ultrasound of the right upper quadrant has emerged as the most commonly used imaging modality for suspected cholecystitis. Meta-analysis of the diagnostic performance of ultrasound in detecting acute cholecystitis indicated an unadjusted sensitivity and specificity of 94% and 78%, respectively.[29] The investigators included in their analysis adjustments for verification bias[30-32] (also called workup bias[33]), which refers to the distorted diagnostic test characteristics observed when the decision to proceed with a gold standard test (eg, cholecystectomy) is affected by the results of preliminary tests such as right upper quadrant ultrasound. Patients with a negative ultrasound result will undergo cholecystectomy only in the setting of extremely typical clinical findings. The consequent loss of patients with atypical clinical presentations reduces the opportunity for false-negative ultrasound results, thus inflating the apparent sensitivity of ultrasound and its associated "rule out" power. Conversely, specificity and the associated "rule in" ability of ultrasound are underestimated.

Adjusting for the effects of verification bias in the above mentioned meta-analysis[29] indicated that ultrasound detects acute cholecystitis with sensitivity of 88% (95% confidence interval [CI], 74%-100%) and specificity of 80% (95% CI, 62%-98%). Sensitivity for the detection of cholelithiasis was comparable, but specificity was higher at approximately 99%. Radionuclide scanning has slightly better test characteristics for the diagnosis of acute cholecystitis, but offers no evaluation of alternative abdominal diagnoses and has the disadvantages of greater inconvenience and patient exposure to radiation.[29] Computed tomography of the abdomen, though useful for the evaluation

of suspected complications and concurrent intra-abdominal conditions, is inferior to ultrasound in the assessment of acute biliary disease.[34,35]

METHODS

The initial electronic search queried the MEDLINE database for the period January 1966 through November 2000 (limited to English-language articles) using the Medical Subject Headings (MeSH) *acute abdomen, abdominal pain, cholecystitis, cholelithiasis, gallbladder,* and *gallbladder diseases*. These terms were then combined with various combinations of MeSH terms, title words, and text words: *physical examination, medical history taking, professional competence, sensitivity and specificity, reproducibility of results, observer variation, diagnostic tests, decision support techniques, Bayes theorem, predictive value of tests, palpation, percussion, differential diagnosis,* and *diagnostic errors*. The Science Citation Index and Cochrane Library were also searched, and a hand search of Index Medicus was conducted for the years 1950 through 1965 using the terms *cholecystitis, acute abdomen,* and *gallbladder*. Bibliographies of identified articles were searched for additional pertinent articles, as were the bibliographies of prominent textbooks of physical examination, surgery, and gastroenterology. An electronic search of MEDLINE was repeated in July 2002 to look for any relevant articles appearing since completion of the more comprehensive search.

Two authors independently abstracted data from the identified studies, and all 3 authors reviewed these data for inclusion. Included studies evaluated the role of a clinical test (including history, physical examination, and basic laboratory tests) in adult patients with abdominal pain or suspected acute cholecystitis. Included studies were also required to report data from a control group of patients subsequently found not to have acute cholecystitis, with sufficient detail to allow construction of 2×2 tables. Finally, studies were required to define cholecystitis on the basis of an adequate gold standard, including surgery, pathologic examination, radio-

graphic imaging (hepatic iminodiacetic acid [HIDA] scan or right upper quadrant ultrasound), or clinical follow-up documenting a course consistent with acute cholecystitis and without evidence for an alternate diagnosis.

Summary measures for the sensitivity of the evaluated components of the clinical examination and basic laboratory tests for cholecystitis were derived from published raw data from the reported studies meeting our inclusion criteria. A random-effects model was used to generate conservative summary measures and CIs for the sensitivity and likelihood ratios (LRs).[36-38] For LRs, a summary measure is reported only when more than 2 studies were identified; otherwise a range was reported.

RESULTS

Of 195 studies identified by our search, 17 evaluated the role of the clinical examination or basic laboratory test in patients with acute abdominal pain and possible acute cholecystitis and also met our inclusion criteria (**TABLE 1**).[39-55] Twelve of these studies[40,42-47,49,51-54] enrolled patients specifically suspected of having acute cholecystitis, with inclusion of many of these studies based on patient referral for radiology testing (ie, HIDA scan or right upper quadrant ultrasound) for the confirmation of a clinical diagnosis. The remaining 5 studies[39,41,48,50,55] enrolled patients presenting with abdominal pain and did not require a specific suspicion of acute cholecystitis for patient inclusion. Each of the 17 studies evaluated a variable number of clinical and laboratory findings included in the workup of suspected cholecystitis, ranging from 1 to 9 parameters per study (**TABLE 2**).

Precision of Signs and Symptoms

Measurements of laboratory parameters and objective clinical signs such as temperature are assumed to have high precision, but the reproducibility of other aspects of the clinical examination for cholecystitis remains largely unknown. In fact, the only study identified as assessing the precision of some aspect of the clinical examination for biliary dis-

ease was an evaluation of the diagnostic value of iridology[56] (iridologists believe that intricate neural connections between major organs and the iris permit diagnosis of general medical conditions through inspection of iris pigmentation patterns[57,58]). In this relatively well-designed study, the accuracy and precision of iridological signs for the diagnosis of cholecystitis were barely distinguishable from values expected by chance alone ($\kappa = -0.06$ to 0.28 for the 10 possible observer pairs).

Unfortunately, analogous studies have not been carried out with conventional clinical maneuvers related to the diagnosis of cholecystitis. In fact, as noted in a previous article in this series,[59] the precision of even the most basic components of the abdominal examination (eg, guarding, rigidity, and rebound tenderness) remains uncharacterized. Poor reproducibility for abdominal examination would erode the assessments of sensitivity and specificity provided by different investigators. Presumably, then, one can infer a certain degree of interrater reliability from the fact that multiple studies demonstrate modest sensitivity for these signs in diagnosing important abdominal conditions.[59] Nonetheless, further assessments of core components of the abdominal examination would be a welcome addition to the literature.

Accuracy of Signs and Symptoms

No single clinical or laboratory finding had a negative LR sufficiently low to rule out the diagnosis of acute cholecystitis (Table 2). One possible exception was right upper quadrant tenderness, with a negative LR of 0.4, though the 95% CI for this summary estimate included 1.0. Moreover, the "rule out" power of this finding may have been artificially inflated by the effects of spectrum and verification bias (discussed below). Elderly patients may be particularly prone to present without signs or symptoms referable to the right upper quadrant.[60]

Similarly, individual symptoms, signs, and laboratory results were without positive LRs sufficiently high to rule in the diagnosis of acute cholecystitis.

In fact, none of the positive LRs were above 2.0, with the exception of the Murphy sign, which was associated with a ratio of 2.8. The 95% CI for this summary estimate included 1.0, but it is worth noting that the use of the Murphy sign was especially prone to verification bias. Thus, the true positive LR might exceed the estimated value.

Limitations of the Literature

The problem of verification (or workup) bias[30-33] was discussed in the section on diagnostic imaging, but likely affected all of the clinical and laboratory findings assessed in this review. Patients with upper abdominal tenderness, fever, abnormal liver function results, or other "typical" findings more commonly undergo further evaluation (eg, diagnostic imaging) for acute cholecystitis than do patients presenting without these findings. The loss of patients with atypical presentations from study samples overestimates sensitivity and underestimates specificity for the findings evaluated. Supplementing the diagnosis of cholecystitis with clinical follow-up would mitigate the effects of verification bias, but only 1 study[39] incorporated clinical follow-up in the diagnostic protocol.

Spectrum bias[61] (or, more recently, spectrum effect[62]) distorts test characteristics in a manner similar to that produced by verification bias, but on the basis of inadequate representation of the relevant disease and disease-free states in the patient samples used to challenge the test of interest. The prevalence of cholecystitis in the study populations was as high as 80% and averaged 41%, in contrast to the prevalence of 3% to 5% among patients presenting with abdominal pain of less than 1 week's duration.[1,2,41]

Table 1. Studies of the Diagnostic Performance of Clinical and Laboratory Findings in Detecting Acute Cholecystitis

Source	Study Period	Selection Criteria	Design	Sample Size	Consecutive Patients	Basis for Diagnosis
Adedeji and McAdam,[39] 1996	1985-1990	Acute abdominal pain and age >70 y	Retrospective	431	Yes	Clinical follow-up
Bednarz et al,[40] 1986	1983-1984	Suspected acute cholecystitis and referred for HIDA scan	Prospective	70	Yes	Surgery (43%) Clinical impression (57%)
Brewer et al,[41] 1976	1971-1972	Abdominal pain	Retrospective	570	Yes	Multiple
Dunlop et al,[42] 1989	1982-1986	Acute abdominal pain and suspected acute cholecystitis	Prospective	270	Yes	Pathology (71%) Clinical impression (29%)
Eikman et al,[43] 1975	Not stated	Suspected acute cholecystitis and referred for radiology testing	Prospective	38	Yes	Surgical (38%) Clinical impression (62%)
Gruber et al,[44] 1996	1990-1993	Positive HIDA scan results and underwent surgery for suspected acute cholecystitis	Retrospective	198	Yes	Pathology
Halasz,[45] 1975	1969-1974	Suspected acute cholecystitis	Retrospective	238	Yes	Surgery (65%) Other (35%)*
Johnson and Cooper,[46] 1995	Not stated	Positive HIDA scan results and underwent surgery for suspected acute cholecystitis	Retrospective	69	No	Pathology
Juvonen et al,[47] 1992	1988-1989	Suspected acute cholecystitis referred for ultrasound	Prospective	129	Yes	Pathology (95%) Ultrasound (5%)
Liddington and Thomson,[48] 1991	Not stated	Abdominal pain	Prospective	142	No	Clinical impression
Lindenauer and Child,[49] 1966	1959-1964	Underwent cholecystectomy	Retrospective	200	No	Pathology
Potts and Vukov,[50] 1999	1992-1995	Abdominal pain requiring operation and age >80 y	Retrospective	117	Yes	Pathology
Prevot et al,[51] 1999	1997-1999	ICU patients with suspected acute acalculous cholecystitis	Prospective	32	Yes	Pathology (50%) Clinical impression (50%)
Raine and Gunn,[52] 1975	1965-1973	Suspected acute cholecystitis and underwent surgery	Prospective	156	Yes	Pathology
Schofield et al,[53] 1986	Not stated	Abdominal pain and suspected acute cholecystitis	Prospective	100	Yes	Gallstones at laparotomy
Singer et al,[54] 1996	1993	Suspected acute cholecystitis and radiology testing completed	Retrospective	100	Yes	Pathology (44%) HIDA scintigraphy (56%)
Staniland et al,[55] 1972	Not stated	Admission for abdominal pain of <1 week	Retrospective	600	No	Surgery

Abbreviations: HIDA, hepatic iminodiacetic acid; ICU, intensive care unit.
*Radiology testing and clinical follow-up, exact proportions not specified.

Ideally, subgroup analysis would generate values for sensitivity and specificity in patient populations with substantially different prior likelihoods of disease.[62] Because available data often do not permit such analysis, one has to make qualitative inferences about the difference between the prior probability of disease in a particular patient and the prevalence in the population used to evaluate the test. For instance, a high prevalence of cholecystitis among study samples reduces the opportunity to detect both false-positive and true-negative results, and thus will overestimate sensitivity and underestimate specificity when the test is applied to patient populations with a lower prevalence of disease. Thus, clinical findings and laboratory tests used to evaluate cholecystitis likely have lower sensitivity but higher specificity than suggested in the available literature. In other words, as with verification bias, spectrum bias produces overestimates of the "rule out" powers of tests for acute cholecystitis and underestimates of their "rule in" powers.

Other limitations to the existing literature include the retrospective design of most studies, modest sample sizes, unblinded assessment of key outcomes and test results, and the variability in criteria for establishing a diagnosis of cholecystitis. The included studies varied between accepting clinicians' diagnostic impressions (usually incorporating imaging results), findings at laparotomy, and pathological findings as the means of diagnosis. Unfortunately, the correlation between clinical and pathological diagnoses of cholecystitis is poor.[63] Gallstones occur commonly enough that their presence, even in the context of inflammatory cells, may be "true but unrelated" with respect to the patient's acute presentation. Overdiagnosis from this and other available gold standards likely resulted in an overestimation of the prevalence of acute cholecystitis, with consequent distortion of the usefulness of clinical and basic laboratory findings. Finally, studies assessing both calculous and acalculous cholecystitis were included in the review. Although these entities share many clinical traits, the nonspecific presentation of acalculous

Table 2. Summary Test Characteristics for Clinical and Laboratory Findings in Included Studies*

Finding	Studies			Summary LR (95% CI)†		Sensitivity (95% CI)	Specificity (95% CI)
	No.	References	No. of Patients‡	Positive	Negative		
			Clinical				
Anorexia	2	41, 55	1135	1.1-1.7	0.5-0.9	0.65 (0.57-0.73)	0.50 (0.49-0.51)
Emesis	4	41, 46, 53, 55	1338	1.5 (1.1-2.1)	0.6 (0.3-0.9)	0.71 (0.65-0.76)	0.53 (0.52-0.55)
Fever (>35 °C)	8	40, 41, 44, 46, 50-53	1292	1.5 (1.0-2.3)	0.9 (0.8-1.0)	0.35 (0.31-0.38)	0.80 (0.78-0.82)
Guarding	2	41, 55	1170	1.1-2.8	0.5-1.0	0.45 (0.37-0.54)	0.70 (0.69-0.71)
Murphy sign	3	39, 46, 54	565	2.8 (0.8-8.6)	0.5 (0.2-1.0)	0.65 (0.58-0.71)	0.87 (0.85-0.89)
Nausea	2	46, 54	669	1.0-1.2	0.6-1.0	0.77 (0.69-0.83)	0.36 (0.34-0.38)
Rebound	4	40, 41, 48, 55	1381	1.0 (0.6-1.7)	1.0 (0.8-1.4)	0.30 (0.23-0.37)	0.68 (0.67-0.69)
Rectal tenderness	2	41, 55	1170	0.3-0.7	1.0-1.3	0.08 (0.04-0.14)	0.82 (0.81-0.83)
Rigidity	2	41, 55	1140	0.50-2.32	1.0-1.2	0.11 (0.06-0.18)	0.87 (0.86-0.87)
Right upper abdominal quadrant							
Mass	4	40, 45, 53, 54	408	0.8 (0.5-1.2)	1.0 (0.9-1.1)	0.21 (0.18-0.23)	0.80 (0.75-0.85)
Pain	5	40, 45, 46, 54, 55	949	1.5 (0.9-2.5)	0.7 (0.3-1.6)	0.81 (0.78-0.85)	0.67 (0.65-0.69)
Tenderness	4	40, 45, 54, 55	1001	1.6 (1.0-2.5)	0.4 (0.2-1.1)	0.77 (0.73-0.81)	0.54 (0.52-0.56)
			Laboratory				
Alkaline phosphatase >120 U/L	4	42, 46, 49, 51	556	0.8 (0.4-1.6)	1.1 (0.6-2.0)	0.45 (0.41-0.49)	0.52 (0.47-0.57)
Elevated ALT or AST§	5	42, 46, 49, 51, 53	592	1.0 (0.5-2.0)	1.0 (0.8-1.4)	0.38 (0.35-0.42)	0.62 (0.57-0.67)
Total bilirubin >2 mg/dL	6	40, 42, 43, 46, 49, 51	674	1.3 (0.7-2.3)	0.9 (0.7-1.2)	0.45 (0.41-0.49)	0.63 (0.59-0.66)
Total bilirubin, AST, or alkaline phosphatase	1	52	270				
All 3 elevated				1.6 (1.0-2.8)	0.8 (0.8-0.9)	0.34 (0.30-0.36)	0.80 (0.69-0.88)
Any 1 elevated				1.2 (1.0-1.5)	0.7 (0.6-0.9)	0.70 (0.67-0.73)	0.42 (0.31-0.53)
Leukocytosis‖	7	41, 44, 46, 50-53	1197	1.5 (1.2-1.9)	0.6 (0.5-1.8)	0.63 (0.60-0.67)	0.57 (0.54-0.59)
Leukocytosis‖ and fever	2	44, 52	351				
Yes				1.6 (0.9-2.8)	0.9 (0.8-1.0)	0.24 (0.21-0.26)	0.85 (0.76-0.91)
No				0.5 (0.4-0.7)	1.6 (1.4-1.8)	0.30 (0.27-0.33)	0.44 (0.34-0.54)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; LR, likelihood ratio.
*One study evaluated C-reactive protein, but was not included since C-reactive protein is not a part of the routine evaluation of patients with abdominal pain or suspected acute cholecystitis.[53] "Pain followed by emesis" was reported in 1 study (positive LR, 2.5 [95% CI, 2.1-3.0]; negative LR, 0.04 [95% CI, 0.04-0.6]).
†Summary measures provided only for findings discussed by more than 2 studies.
‡May not equal sums of Ns in Table 1 because not all studies applied all tests to all patients.
§Greater than upper limit of normal (ALT: 40 U/L; AST: 48 U/L).
‖White blood cell count >10 000/mL.

cholecystitis likely eroded the value of several clinical findings.

Combinations of Findings and the Clinical "Gestalt"

Even with the above limitations, it seems unlikely that individual clinical or laboratory findings have positive or negative LRs of sufficient magnitude to play a decisive role in the diagnosis of acute cholecystitis. Thus, one might look to combinations of clinical signs and symptoms to facilitate, confirm, or exclude the diagnosis of cholecystitis. Unfortunately, only 3 included studies[42,44,52] specifically evaluated the value of such combinations. Two studies evaluated the combination of fever and leukocytosis; the third reviewed various combinations of liver function tests. Assessments of the LRs of the above combinations demonstrated no benefit over their individual components, suggesting that these tests did not function independently of one another. Indeed, fever and leukocytosis may be seen as different manifestations of the same underlying process of nonspecific inflammation, so it is not surprising that combining them provided no synergistic diagnostic value. Similarly, right upper quadrant pain and the Murphy sign likely reflect the same underlying pathophysiologic process (ie, local inflammation and peritoneal irritation), so that these findings would not be expected to function independently of one another.

Although the existing literature does not identify specific clinically useful combinations of findings, the impact of such combinations can be estimated using available data. In 2 randomized trials of early vs delayed cholecystectomy,[13,14] laparotomy failed to confirm the preoperative diagnosis of acute cholecystitis in 5 of 99 patients (95% CI, 1.9%-11.9%)[14] and in 0 of 104 patients (95% CI, 0%-4.4%).[13] Given a likely bias toward confirming the preoperative diagnosis, let us assume that the actual false-positive rate for the clinical diagnosis of cholecystitis is higher (eg, 15%) than suggested by these values.

A 15% false-positive rate would imply an 85% posttest probability for all

clinical, laboratory, and radiological tests. We know that ultrasound of the right upper quadrant has a sensitivity and specificity of 88% and 80%, respectively.[29] Working backward, we can infer that the composite clinical evaluation generates a pretest probability of approximately 60% before the results of ultrasound are obtained. This posttest probability of 60% for the clinical suspicion of cholecystitis reflects the diagnostic power of the clinical evaluation prior to ultrasound as well as the pretest probability. At this stage in the diagnostic process, the pretest probability reflects the prevalence of the diagnosis, which is approximately 5% among patients presenting to the emergency department with abdominal pain.[1,2,41] Thus, the clinical diagnosis of acute cholecystitis formulated on the basis of history, physical examination, and basic laboratory testing must increase the pretest probability from 5% to 60%.

Achieving this increase in pretest probability requires that the gestalt comprising certain clinical and laboratory findings have a positive LR on the order of 25 to 30. To put this range in perspective, "typical angina" has a positive LR of 115 for the diagnosis of coronary artery stenosis greater than 75% in adult men. Nonsloping depression of the ST segment of at least 2.5 mm during exercise electrocardiography has a positive LR of 39 for the same diagnosis.[64] Thus, our estimate for the diagnostic usefulness of the clinical gestalt in diagnosing acute cholecystitis, approximate and speculative as it is, confirms the impression of many clinicians that the overall clinical assessment plays a crucial role in arriving at a diagnosis.

It is tempting to supplement the existing literature by asking experts for their opinion on which specific findings drive the clinical impression for or against acute cholecystitis. Unfortunately, discerning the key elements of the clinical assessment can prove deceptive, even for experienced clinicians. For instance, a recent clinical model for the prediction of pulmonary embolism omits hypoxemia and pleurisy from the algorithm for determining pretest probability.[65,66] Simi-

larly, many of the classic descriptors of angina have surprisingly little impact on the assessment of chest pain.[67] This dissociation between commonly accepted harbingers of disease and evidence-based determinants of disease probability undermines the role of expert opinion in identifying key clinical findings even for common conditions. Consequently, tempting as it is to open the "black box" of the clinical gestalt for cholecystitis, doing so will require further study of specific clinical findings or, more likely, combinations of findings.

SCENARIO RESOLUTION

Your differential diagnosis for the patient's presentation includes viral hepatitis, cholecystitis, and gallstone pancreatitis. To validate your impression and help establish the relative likelihood of each, you ask the emergency department attending physician to evaluate the patient. She regards the likelihood of cholecystitis as high enough to warrant diagnostic imaging. In fact, her clinical impression is that cholecystitis is the leading diagnosis, so she recommends urgent right upper quadrant ultrasound. The ultrasound subsequently reveals the presence of gallstones, gallbladder wall thickening, and a sonographic Murphy sign. These findings, in the context of the patient's presentation, virtually confirm the diagnosis of acute cholecystitis.[68]

THE BOTTOM LINE

The existing literature identifies no single finding with sufficient diagnostic power to establish or exclude acute cholecystitis without further testing (eg, right upper quadrant ultrasound). Combinations of certain symptoms, signs, and laboratory results likely have more useful LRs, and presumably inform the diagnostic impressions of experienced clinicians. Future research may allow the development of prediction rules that combine basic demographics with clinical findings to distinguish patients who require no further testing from those who require continued diagnostic evaluation, as is currently possible with the evaluation of suspected pulmonary embolism.[66,69] Until then, the clinical evalu-

ation of patients with abdominal pain suggestive of cholecystitis will continue to rely heavily on the clinical gestalt and diagnostic imaging.

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