The Diagnosis of Acute Cholecystitis

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Introduction

Acute cholecystitis is an inflammatory condition of the gallbladder resulting from a spectrum of pathophysiologic processes. While the diagnosis of AC is frequently straightforward, in some settings it can be quite complex. Acute cholecystitis is most commonly the result of acute obstruction of the cystic duct by biliary stones or cholelithiasis, termed calculous cholecystitis. Acute cholecystitis may also occur in settings in which obstruction of the cystic duct by stones is not the etiologic process, thus classified as acalculous cholecystitis. Occasionally, acute cholecystitis may develop in the setting of chronic inflammation and scarring of the gallbladder (chronic cholecystitis) altering common radiographic findings and confounding the diagnosis of acute cholecystitis. Both calculous and acalculous acute cholecystitis may progress to gangrenous cholecystitis with an elevated risk of free perforation and perioperative complications.

The diagnosis of most cases of typical calculous acute cholecystitis can usually be achieved with a high degree of accuracy with the combination of clinical presentation and diagnostic imaging. The signs and symptoms that suggest a diagnosis of acute calculous cholecystitis are due to one of the two pathophysiologic processes (1) contraction of the gallbladder against obstruction to biliary outflow causing biliary colic and (2) inflammation of the gallbladder that occurs secondary to the obstruction. As the condition progresses, the symptoms typically evolve. As the process becomes more severe and prolonged, contraction of the gallbladder and symptoms of biliary colic subside and symptoms of local inflammation predominate. As the severity progresses further, systemic symptoms advance. However, the signs, symptoms, and laboratory changes produced by the inflammatory process of acute cholecystitis are nonspecific and other inflammatory conditions involving organs in the right upper quadrant of the abdomen can mimic cholecystitis. Processes that may mimic acute cholecystitis and should be considered and excluded from the differential diagnosis include hepatitis, pancreatitis, or peptic ulcer disease. Additionally, establishing the diagnosis in certain patient populations may be more complex and difficult. Critically ill patients with acalculous acute cholecystitis and patients with comorbid diseases that alter the signs and symptoms of

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acute inflammation, such as those with diabetes or immunosuppression may be more difficult to diagnose. A delayed diagnosis of acute cholecystitis may lead to increased morbidity and mortality due to progression to gangrenous cholecystitis, perforation, and resultant increased operative complexity.

Historically, the diagnosis of acute cholecystitis was based almost solely on clinical findings. Chief among these was the Murphy's sign [1]. Unfortunately, many patients will not present with this clinical finding. Sensitivity of the Murphy's sign for acute cholecystitis is highly variable. Moreover, there is no one biochemical marker specific for acute cholecystitis. Fortunately, the advent of and subsequent improvement in various imaging modalities has aided the evaluation of the biliary tract. Ultrasonography (US), computed tomography (CT), and hepatobiliary scintigraphy are now commonly available and used in the diagnosis and evaluation of patients with right upper quadrant (RUQ) pain. Magnetic resonance imaging (MRI) is also used in selected patients and in some cases may provide additional functional information when hepatobiliary contrast is utilized. To address the variable physical exam findings, lack of a specific laboratory test, and the emergence of imaging technology, objective diagnostic criteria for the diagnosis of acute cholecystitis were established by an international consensus conference in 2007 and subsequently validated (termed the Tokyo Guidelines) [2, 3].

The Tokyo Guidelines

In 2003, the Japanese Society of Hepato-Biliary-Pancreatic Surgery, along with the Japanese Biliary Association and the Japanese Society for Abdominal Emergency Medicine formed a working group to develop guidelines for the management of cholangitis and cholecystitis. In 2006, an International Consensus Meeting was held in Tokyo, Japan. From this meeting came the Tokyo Guidelines for the Management of Acute Cholangitis and Cholecystitis. The so-called Tokyo Guidelines (TG13) was subsequently revised in 2013 to reflect the increasing importance of diagnostic imaging [4, 5].

Table 3.1 Diagnostic criteria for acute cholecystitis, according to Tokyo Guidelines[a]

• *Local symptoms and signs of inflammation* – Murphy's sign – Pain or tenderness in the right upper quadrant – Mass in the right upper quadrant
• *Systemic signs of inflammation* – Fever – Leukocytosis – Elevated C-reactive protein level
• *Imaging findings* – A confirmatory finding of acute cholecystitis on imaging (US, CT, or HIDA)
Suspected diagnosis The presence of one local sign of inflammation and one systemic sign of inflammation
Definite diagnosis The presence of one local sign or symptom, one systemic sign, and a confirmatory finding on an imaging test **Must rule out acute hepatitis, chronic cholecystitis, and other acute abdominal diseases

[a]Data are from Takada et al. and Hirota et al.

Diagnostic criteria described in the Tokyo Guidelines consist of three components: (A) local signs of inflammation, (B) systemic signs of inflammation, and (C) imaging findings of acute cholecystitis (see Table 3.1). Local signs of inflammation are predominantly limited to physical exam findings of right upper quadrant inflammation. These findings include positive Murphy's sign and RUQ mass, pain or tenderness. As severity progresses, systemic signs of inflammation also progress. Systemic signs of inflammation included in the guidelines are fever, leukocytosis, and elevated C-reactive protein (CRP). While transmural inflammation of the gallbladder may involve adjacent liver parenchyma and produce a mild elevation in liver function tests, such abnormalities do not significantly aid in establishing the diagnosis. More than a mild elevation in liver functions tests should suggest alternative diagnoses such as hepatitis or coexisting cholangitis. Imaging findings of acute cholecystitis are the final, and most important, component of the Tokyo Guidelines. Included in this are findings on US, CT, and scintigraphy that are consistent with acute cholecystitis. Each of these imaging

modalities is discussed later in more detail. However, per the Tokyo Guidelines definitions, ultrasonographic evidence of acute cholecystitis consists of the presence of gallbladder wall thickening, pericholecystic fluid, or ultrasonographic Murphy's sign. A suspected diagnosis of acute cholecystitis should be considered when local signs of inflammation are present along with one systemic sign of inflammation. A definite diagnosis can only be confirmed with a suspected diagnosis plus an imaging finding of acute cholecystitis. However, prior to applying Guidelines criteria, other causes of right upper quadrant pain must be ruled out including hepatitis, pancreatitis, peptic ulcer disease, chronic cholecystitis, or other sources of abdominal pain. A recent validation study of the TG13 guidelines demonstrated a sensitivity of 91.2 %, specificity of 96.9 %, and an accuracy of 94 % [4]. However, limited published data are available to quantify accuracy of the Tokyo Guidelines when the presence of other disease processes may coexist or remain to be excluded or for clinical settings where any of the three components (local inflammation, systemic inflammation, or imaging) may be altered. Limitations of the Tokyo Guidelines include the underdiagnoses of patients with few systemic symptoms and the infrequent utilization of C-reactive protein in the United States [6].

Presentation

Symptom history is an important part of the diagnosis of acute cholecystitis as it can identify at-risk patients. It may also help to eliminate other options from the differential diagnosis. Gallstones or biliary sludge are the most common cause of acute cholecystitis due to cystic duct obstruction [7]. Risk factors for gallstones include advancing age, obesity, rapid weight loss, female gender, and elevated estrogen levels (pregnancy, parity, and estrogen replacement therapy). Other causes of cystic duct obstruction include parasites, masses, and foreign bodies. Acute cholecystitis without evidence of cholelithiasis is referred to as acalculous cholecystitis. This is a challenging diagnosis that is discussed later in this chapter.

Clinical presentation of patients presenting with acute cholecystitis most commonly includes right upper quadrant and/or epigastric pain, occurring in 72–93 % of cases of acute cholecystitis [8–11]. Often this pain is intermittent or may be described as coming in waves. This intermittent, crampy RUQ pain is referred to as biliary colic. Nausea and vomiting are also very common, occurring in 62–83 % of cases [8, 9, 12, 13]. Symptoms can frequently occur in the postprandial period, particularly after meals high in fat. Fevers are less common with only 10–30 % manifesting temperatures over 38 °C [12, 14, 15].

The physical exam finding most connected to the diagnosis of acute cholecystitis is the Murphy's sign. This exam finding was first described in 1903 by John B. Murphy as significant pain to palpation over the gallbladder in the RUQ. He noted "the most characteristic and constant sign of gall-bladder hypersensitiveness [sic] is the inability of the patient to take a full, deep inspiration, when the physician's fingers are hooked up beneath the right costal arch below the hepatic margin" [1]. Subsequent studies have demonstrated this finding to be a reliably specific test, but variable in sensitivity. Specificity of a Murphy's sign for the diagnosis of acute cholecystitis ranges from 79 to 96 % [3, 8, 16]. Inflammatory processes not caused by cholecystitis but that involve the visceral peritoneum overlying the gallbladder or inflammation of the liver capsule can produce findings consistent with a positive Murphy's sign. The sensitivity of a Murphy's sign is fairly low, reported as low as 20.5 % to as high as 65 % [3, 16]. Thus, its use as a diagnostic test can result in a high rate of false negative findings.

Laboratory Tests

For the diagnosis of acute cholecystitis, there is no biomarker that specifically correlates with gallbladder pathology. Markers of generalized inflammation in combination with other clinical and imaging findings can increase the reliability of the diagnosis of acute cholecystitis. Leukocytosis and elevated CRP are most commonly employed.

Mild leukocytosis (over 10,000 cells/μL) is suggestive of systemic inflammation. Higher WBCs are more likely to be associated with more severe disease like gangrenous cholecystitis. However, studies have not clearly delineated where the transition from acute cholecystitis to gangrenous cholecystitis occurs. White Blood Cell counts over 13,000, 15,000, and 17,000 cell/μL have all been associated with increased risks of gangrenous cholecystitis [17–21]. CRP is also present in conditions of systemic inflammation. Values over 3 mg/dL are consistent with inflammatory conditions. When elevated CRP is combined with positive ultrasound findings for acute cholecystitis, sensitivity is 97 % for acute cholecystitis, with 76 % specificity [22]. Similar to leukocytosis, higher elevations of CRP correlate with greater likelihood of the existence of gangrenous cholecystitis [21, 22]. Transmural inflammation of the gallbladder may involve adjacent liver parenchyma that may produce a mild elevation in gamma-glutamyltranspeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin but such abnormalities do not significantly aid in establishing the diagnosis. Significant elevation in liver functions tests are not due to inflammatory processes predominantly involving the gallbladder as the organ is functionally separated from the liver. Significant elevation of transaminases or bilirubin should prompt evaluation of alternative pathology such as hepatitis or coexisting cholangitis.

Imaging

Significant advancements in the diagnosis of acute cholecystitis have occurred with improvements in imaging technology. The majority of cases of acute calculous cholecystitis can reliably be established in a straightforward fashion with the use of ultrasound or computed tomography. Less frequently MRI and/or Tc-HIDA scans may be used to aid in the diagnosis. Rarely, in certain complex settings, the diagnosis (or its exclusion) may remain uncertain despite these advances. Each test has particular attributes as described below.

Ultrasound

Ultrasound is probably the most frequently used diagnostic imaging modality for acute cholecystitis. It should be considered the first imaging option for all suspected cases of acute cholecystitis. Advantages of ultrasound are multiple. It is often immediately available in the Emergency Department and can be even brought to the patient's bedside. It is a relatively cheap study making it accessible to more hospitals and patients. Findings are not affected by elevated liver function tests. Ultrasound can visualize gallstones (Fig. 3.1), which can be difficult to identify using CT or HIDA scan, is quick and noninvasive, and does not expose the patient to ionizing radiation. There are a few clear limitations for ultrasound; it is well known to be operator dependent and gallbladder visualization can be limited by patient body habitus and by bowel gas between the ultrasound probe and the gallbladder.

While acute cholecystitis on ultrasound can have a variable appearance, there are a few findings that are considered indicative of AC. Findings include the concurrent presence of thickened gallbladder wall (≥5 mm), pericholecystic fluid, and a sonographic Murphy's sign. Other findings which may also indicate AC include gallbladder distention/enlargement, gallstones, debris echo or sludge, and gas within the gallbladder wall. A sonographic Murphy's sign is the finding of pain elicited by pressing on the gallbladder with the ultrasound probe during ultrasound exam. Because of the ability to accurately press over the gallbladder, the sonographic Murphy's sign can be used to differentiate between other causes of RUQ pain that may manifest with a conventional Murphy's sign (e.g., perforated duodenal ulcer). Gallstones, while considered the cause of about 90 % of acute cholecystitis cases, are not diagnostic of AC. They are frequently present in the non-inflamed gallbladder and can even be a cause of a falsely positive sonographic Murphy's sign.

Ultrasound has demonstrated good sensitivity in multiple studies. Meta-analysis by Keiwiet showed sensitivities ranging from 50 to 100 % with an overall sensitivity of 81 %. Specificities

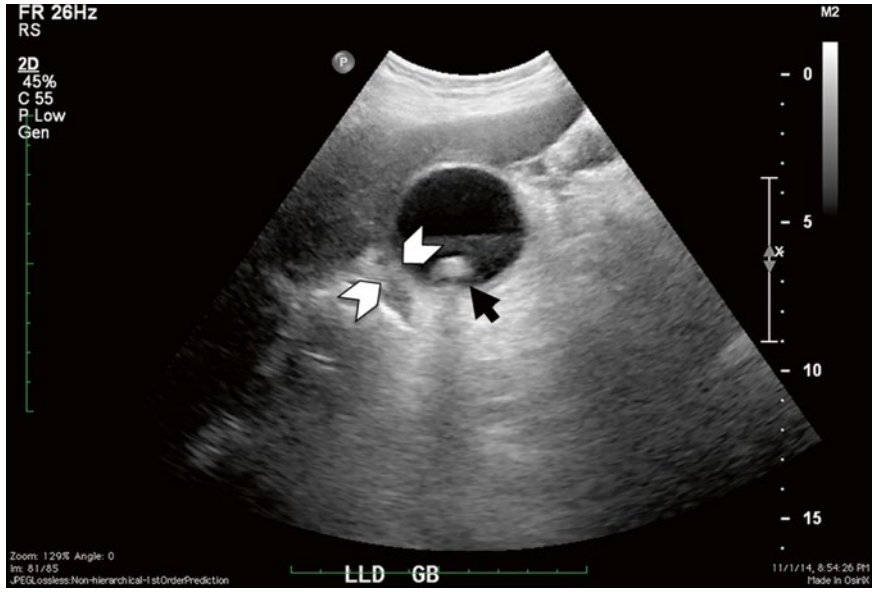

Fig. 3.1 US image showing a GB calculous (*arrow*) demonstrating posterior acoustic shadowing. Sonographic findings in AC include thickened gallbladder wall (between *white chevrons*), pericholecystic fluid, and a sonographic Murphy's sign. Gallbladder distention, gallstones, and debris echo or sludge are also frequently seen in AC

were shown to be a bit better with an overall specificity of 83 %, despite a range of 30–100 % [23]. Sonography by emergency department (ED) physicians has also proven to be reliable in the detection on acute cholecystitis. ED physician-performed US was shown in a study of 116 patients to have a sensitivity of 92 %, specificity of 78 %, and an 86 % accuracy when compared with radiologist-performed ultrasound [24]. More recently, 96 % sensitivity and 79 % specificity was noted on ED physician-performed US when compared to surgical pathology. Additionally, this study noted an 85.5 % rate of agreement when compared with blinded radiologist reading [25]. Sensitivities and specificities in head-to-head studies are comparable as well. In a study comparing the US diagnosis of AC by ED physicians and radiologists, similar sensitivities (87 % vs. 83 %, respectively) and specificities (82 % vs. 86 %, respectively) were reported [26].

In all of these studies, it is important to note that the ED physicians were trained or certified in ultrasonography. Also, while in these studies, the ability to detect acute cholecystitis was outstanding, the clinicians in these studies may have represented a particularly experienced and proficient sample. In light of that, the gold standard remains ultrasound interpreted by trained radiologist. However, in clinical settings with limited radiology availability, ED physician-performed ultrasound may be considered. Ultrasound is most effective when utilized, not in isolation, but in combination with other clinical and laboratory findings suggestive of inflammation. For patients with suspected acute cholecystitis, US plus elevated CRP showed a sensitivity of 97 % [22] for AC. The Tokyo Guidelines themselves are based on the idea of combining imaging findings of acute cholecystitis with clinical findings of inflammation.

Computed Tomography (CT Scanning)

CT scanning is a common imaging modality in patients with abdominal pain. It can differentiate other causes of RUQ pain. CT scanning is available in almost every hospital and has significantly decreased operator dependence compared to

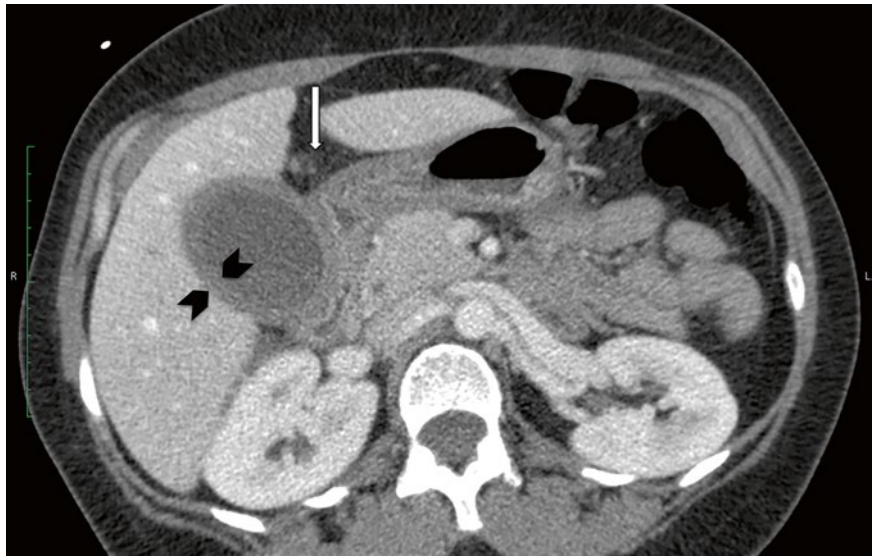

Fig. 3.2 Axial CT image of acute cholecystitis. Gallbladder distention, wall thickening (*chevrons*), and pericholecystic stranding (*white arrow*) are all visible and are findings consistent with AC

ultrasonography. Improvements in technology have led to faster imaging speeds with improved image quality and decreased artifact. Also, the increased anatomic coverage area imaged allows for broader diagnostic capabilities and can detect abdominal pathology outside the right upper quadrant. CT scanning also exhibits superiority over ultrasonography in detecting gastric and bowel pathology. In many centers, CT scanning can diagnose gall bladder disease before the symptoms localize to the right upper quadrant. However, these advantages come at the cost of increased radiation exposure and other side effects. Intravenous iodinated contrast exposure can potentially lead to anaphylaxis and some risk of renal impairment. Lastly, when compared with sonography, CT scanning is more expensive and requires technology that is not portable.

Findings of acute cholecystitis on CT scan (Fig. 3.2) are similar to those seen on ultrasound. Positive findings of the disease include gallbladder wall thickening >3 mm, pericholecystic fat stranding, and gallbladder distention [27]. Pericholecystic fluid, subserosal gallbladder edema, and high attenuation gallbladder can also be visualized, but less commonly [27]. Gallstones may also be visualized depending on the composition and size of the gallstones, but the presence of gallstones may often present in the absence of acute cholecystitis.

CT may not be an effective screening modality for acute cholecystitis. There is a paucity of data regarding the sensitivity of CT for AC diagnosis. In a comparative study with US in 117 patients, CT was shown to have 39 % sensitivity and 93 % specificity [28] and was significantly worse than US, which had a sensitivity and specificity of 83 % and 95 %, respectively. Negative predictive value was good for CT (89 %) but was still lower than US (97 %). The authors concluded that US is a better initial imaging study and that CT should be reserved for patients with a wider differential diagnosis and/or nonstandard symptomatology.

Hepato-Iminodiacetic Acid Scintigraphy

Hepato-Iminodiacetic Acid (HIDA) imaging is an attractive option for the diagnosis of AC as it is highly sensitive with good specificity. The modality is not operator dependent and it can often differentiate between acute and chronic

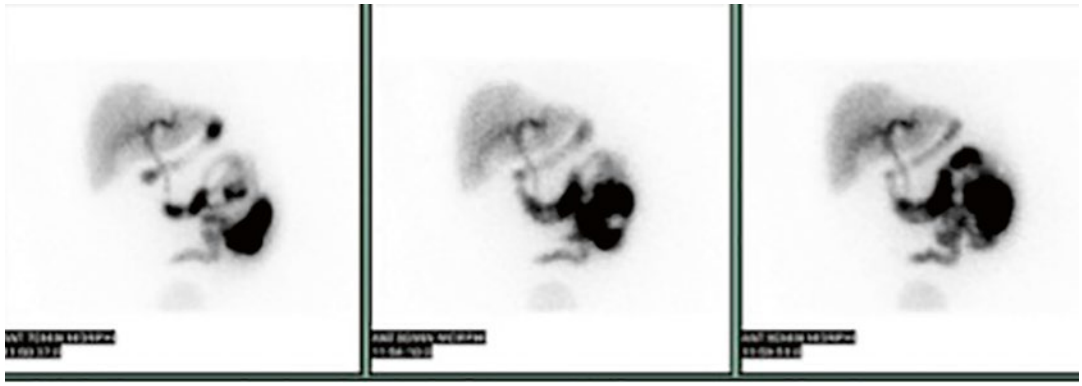

Fig. 3.3 HIDA scan showing no filling of gallbladder after delayed images. Failure to fill gallbladder with radiotracer after 60 min is abnormal but not diagnostic of AC. Findings consistent with AC include failure to fill within 3–4 h without morphine or within 90 min after administration of low-dose morphine at 60 min

cholecystitis, a feature that ultrasonography can often fail to do. Normal findings relate to the rapid filling of the gallbladder with radiotracer and passage into the duodenum which should occur within 30 min. Low sphincter of Oddi pressure can delay filling in some normal gallbladders but can be overcome by administering a low dose of morphine. Failure of the gallbladder to fill within 60 min is abnormal but not diagnostic of acute cholecystitis. The absence of any filling after 3 or 4 h delayed images qualifies as a diagnostic study (Fig. 3.3). Also considered a positive study is no filling after 90 min when morphine was administered at 60 min. These delayed images confirm no delayed filling of the gallbladder. This indicates cystic duct obstruction and is highly sensitive for AC. Chronic cholecystitis can also cause cystic duct obstruction, but much less commonly.

However, HIDA imaging also possesses some disadvantages. This study generally requires a period no oral intake for 3–4 h before the study. Then, the study itself can take up to 3–4 h to complete depending on how rapidly the radiotracer transits into the gallbladder. The first hour of the study is very labor intensive as it requires taking one radiographic image per minute for 60 min. The labor-intensive nature of the study often makes it unavailable outside of normal workday hours. Additionally, the study only gives information regarding the biliary tract. The accuracy of HIDA scanning is dependent on appropriate hepatic clearance and can be affected by altered liver function. Prolonged NPO status or parenteral nutrition can give false positives. Lastly, HIDA scanning exposes patients to ionizing radiation albeit at much lower doses than an abdominopelvic CT scanning and is still discouraged in pregnant females.

Meta-analysis incorporating 40 studies and nearly 4100 patients demonstrated an overall sensitivity of 96 % (95 % CI: 94–97 %) [23]. Further analysis showed that direct comparison to ultrasonography occurred in 11 studies with 1199 total patients. Sensitivity and specificity of scintigraphy in acute cholecystitis were both shown to be significantly higher ($p < .001$) than that of ultrasound (94 % vs. 80 % and 89 % vs. 75 %, respectively) [23]. Chatziioannou demonstrated that overall accuracy is higher with HIDA (92 %) than US (77 %) in a study of 107 patients with suspect AC who underwent both imaging modalities [29]. However, in combination, HIDA and US are exceedingly sensitive for diagnosing acute cholecysitis with a reported sensitivity of 97.7 % [30].

Magnetic Resonance Imaging

Previously, MRI was not a popular imaging modality for suspected acute cholecysitis. MRI was a long study that was expensive for patients and not readily available after hours at most

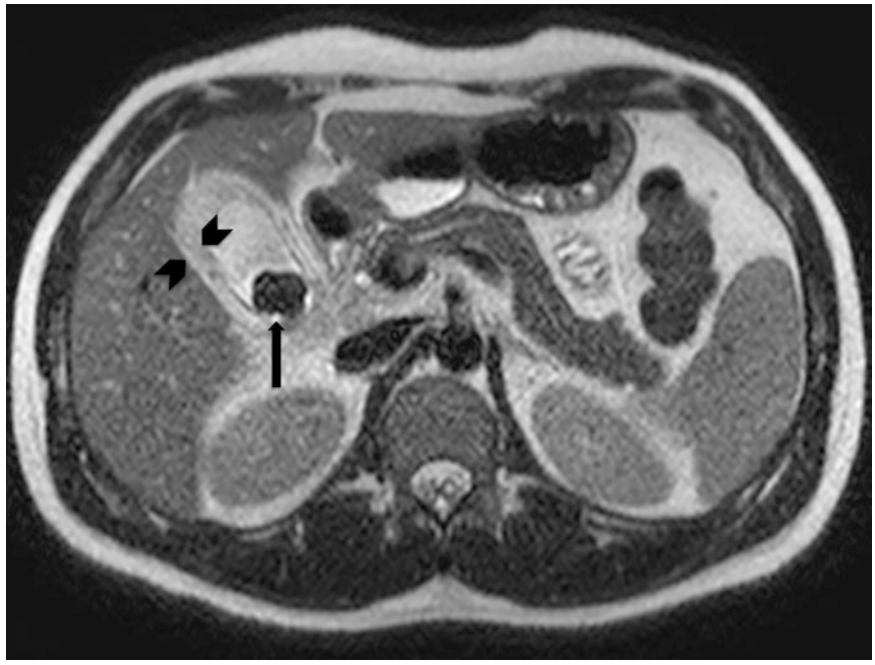

Fig. 3.4 T2 weighted MRI image without fat saturation showing cholelithiasis and acute cholecystitis. Gallstone indicated by *arrow*. Gallbladder wall thickening (between *chevrons*), gallbladder distention and pericholecystic stranding are common findings in AC

institutions. Additionally, many patients can develop discomfort or outright claustrophobia in the MRI scanner. Due to the danger of the magnet of the MRI machine, critically ill patients or those needing frequent access are not candidates for MRI scanning. Increasingly, however, concerns about radiation exposure have led to the reexamination of MRI as imaging option and MRI is safe in pregnancy. In other venues, MRI has become the imaging modality of choice for hepatobiliary, pancreatic, and pelvic pathology. Scanning protocols have been developed that can now complete an abdominal study in 15–30 min [31]. Sensitivity (85 %) and specificity (81 %) fall in between CT and US [23]. As with CT imaging, MRI findings of gallbladder wall thickening, pericholecystic fat stranding, and gallbladder distention are characteristic of acute cholecystitis (Fig. 3.4). Currently, MRI is most used for the detection of acute cholecystitis for those with ambiguity or a contraindication to one of the other modalities or those where additional information is required on hepatobiliary pathology.

Severity Assessment and Predicting Gangrenous Cholecystitis

Upon establishing the diagnosis of AC, determination of the severity of disease process aids in clinical judgment regarding the management of individual patients. The Tokyo Guidelines recommend the use of a three grade system: Grade I or mild AC occurs in a healthy patient with no organ dysfunction and mild inflammatory changes of the gallbladder; Grade II or moderate acute cholecystitis is present when any of several conditions are met—WBC > 18,000 cell/μL, palpable tender mass in the right upper abdominal quadrant, duration of symptoms longer than 72 h, or evidence of marked local inflammatory changes; and Grade III or severe AC is present when evidence of organ dysfunction is present [2]. While no significant prospective data provide information regarding the incidence of patients presenting with acute cholecystitis in the three severity categories, the large majority of patients appear to present as Grade I [6].

As the inflammatory process advances, acute cholecystitis may develop into gangrenous cholecystitis, with transmural inflammation, loss of mucosa, and necrosis of the gallbladder wall [21, 32]. Progression to gangrenous cholecystitis is associated with significantly greater requirement for conversion to open cholecystectomy, postoperative morbidity, and mortality when compared with uncomplicated acute cholecystitis and evidence suggests that this can be reduced by early diagnosis and treatment [33–36]. The incidence of gangrenous cholecystitis in patients with acute cholecystitis ranges from 2 to 41 %, but nearly half of cases of gangrenous cholecystitis are unsuspected preoperatively and no clinical or radiographic criteria consistently identify patients with this condition [19–21, 32, 34, 35]. As the gallbladder undergoes necrosis, local signs of inflammation such as a Murphy's sign diminish and may be completely absent. Identifying those patients at high risk of GC is important for early intervention. Several factors have been shown to be associated with gangrenous versus non-gangrenous cholecystitis in univariate and multivariate analysis including: Age, diabetes mellitus, heart rate, WBC, C-reactive protein, gallbladder wall thickness, and the presence of pericholecystic fluid [21, 32, 35]. Measurements and unadjusted odds ratio for each parameter are shown in Table 3.2.

Table 3.2 Preoperative risk factors for gangrenous cholecystitis

Parameter	Measure	Odds ratio[a]
Age	>45 years old	3.2[b]
	>50 years old	3.5[c]
Diabetes mellitus		2.8[c]
Heart rate	>90 beats per minute	2.8[b]
WBC	≥13,000 cells/μL	2.8[b]
	≥15,000 cells/μL	4.4[c]
C-reactive protein	>200 mg/dL	1.02[d,e]
Gallbladder wall thickness	>4.5 mm	3.2[b]

[a]Unadjusted value
[b]Wu, B. HPB. 2014; 16:801–806
[c]Fagan, S.P. Am J Surg. 200; 186:481–485
[d]Mok, K.W.J. Int J Surg. 2014; 12:649–653
[e]For each unit above 200 mg/dL

Two separate studies have developed predictive models for the presence of gangrenous versus non-gangrenous AC using similar but not identical variables [20, 35]. Nguyen and colleagues used diabetes mellitus, WBC, pericholecystic fluid, ALT ≥ 50 U/L, and alkaline phosphatase ≥ 200 U/L in a complex model to estimate the risk of gangrenous cholecystitis, generating an impressive area under the ROC curve of 88.9 % [20]. In a more recent study, Wu and colleagues developed a simple scoring system using only four factors to create a 0–5 point scale as shown in Table 3.3 [35]. Patients with a score of 0 had a 2 % risk of GC and patients with a score of 5 had a 65 % chance of GC, with the model achieving an area under the ROC curve of 0.77. Mok and colleagues examined C-reactive protein as a single marker and determined that CRP of ≤200 U/L had a 100 % negative predictive value to GC [21]. None of the studies have been validated in larger prospective studies and none have assessed the combined use of all measures determined to be independently related.

A few radiographic findings are suggestive of complicated gallbladder disease. These features are inconsistently found in advanced stage disease and are associated with low sensitivities but high specificities for complicated cholecystitis. One described finding is the so-called *rim sign* noted on HIDA (Fig. 3.6). The rim sign is the increased uptake of radiotracer in the liver adjacent to the gallbladder fossa combined with non-filling of the gallbladder itself [37]. This finding is present in about 25–35 % of cases of AC and has demonstrated a strong specificity for advanced gallbladder disease including gangrenous cholecystitis and even gallbladder perforation [38, 39]. CT, US, and MRI can identify changes suggestive

Table 3.3 Wu scale to differentiate gangrenous cholecystitis from acute cholecystitis

A score over 5 suggests gangrenous cholecystitis	
Age	≤45 = 0
	46 to ≤65 = 1
	>65 = 2
Heart rate	>90 bpm = 1
WBC	>13,000 = 1
Gallbladder wall thickness	>4.5 mm = 1

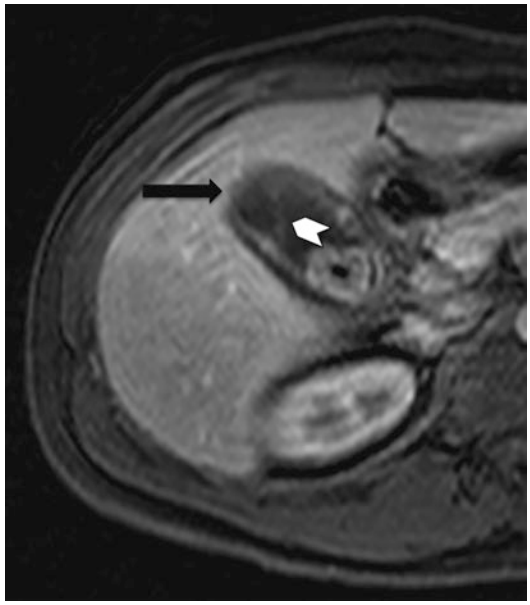

Fig. 3.5 T1 weighted axial image following contrast administration in patient with gangrenous cholecystitis. Chevron indicates an intraluminal membrane and *arrow* identifies a defect in wall enhancement

of complicated cholecystitis (Fig. 3.5), such as intraluminal membranes, gas in wall or lumen, and asymmetric wall thickening [40]. These features are somewhat nonspecific and can represent gangrenous cholecystitis, emphysematous cholecystitis, or even gallbladder perforation. Despite not being consistently found in advanced disease, the presence of any of these changes should heighten the suspicion of advanced stage gallbladder disease.

The Difficult Diagnosis

Certain patient factors and clinical settings can significantly confound and delay the diagnosis of acute cholecystitis, increasing the risk of complication. Unfortunately, limited data are available to quantify the diagnostic accuracy in these particular populations. Advanced age, immunosuppression, diabetes mellitus, preexisting neurologic impairment, and acalculous acute cholecystitis in the critically ill are all factors that may contribute to diagnostic dilemma and uncertainty.

For a variety of reasons, delays in diagnosis abound in elderly patients with acute cholecystitis [6, 41, 42]. Elderly patients have a greater frequency of presentation in which no Murphy's sign is present [41]. Physical examination and laboratory indexes may be in the normal range, fever may be more frequently absent and the only symptoms may be a change in mental status or decreased food intake [6, 41, 42]. As discussed above, age is an independent factor for the development of gangrenous cholecystitis. Thus, a high index of suspicion and an assertive approach to the diagnosis must be maintained. Similar to the elderly population, patients with immunosuppression, diabetes mellitus, or preexisting neurologic impairment may all have limited local signs and symptoms of acute cholecystitis. Blunting of the inflammatory response may allow progression to gangrenous acute cholecystitis without ever having right upper quadrant pain and tenderness and a more frequent progression to severe acute cholecystitis and sepsis [35].

Acalculous acute cholecystitis in the critically ill population is frequently difficult to diagnose with adequate certainty and may require drainage of the gallbladder to exclude its presence. Critically ill patients may have many confounding factors including multiple reasons for pain, fever, and leukocytosis. Critically ill patients may have no ability to corroborate findings while sedated, intubated, and/or unconscious in an intensive care setting. During critical illness, hepatic function may be altered and abnormal liver function assays occur unrelated to the presence of biliary tract pathology.

Although ultrasound, CT scanning, and HIDA scans (Figs. 3.6 and 3.7) play a significant role in the diagnosis of acalculous acute cholecystitis in the critically ill patient, an understanding of the physiologic changes that occur during critical illness and how these changes may alter radiographic findings is essential to appropriately interpreting each in this complex setting. During critical illness, particularly if the patient is fasted for a prolonged period, the gallbladder may passively fill with bile and become distended. The finding of gallbladder distension, therefore, may or may not have diagnostic significance. Additionally, the fluid resuscitation that is

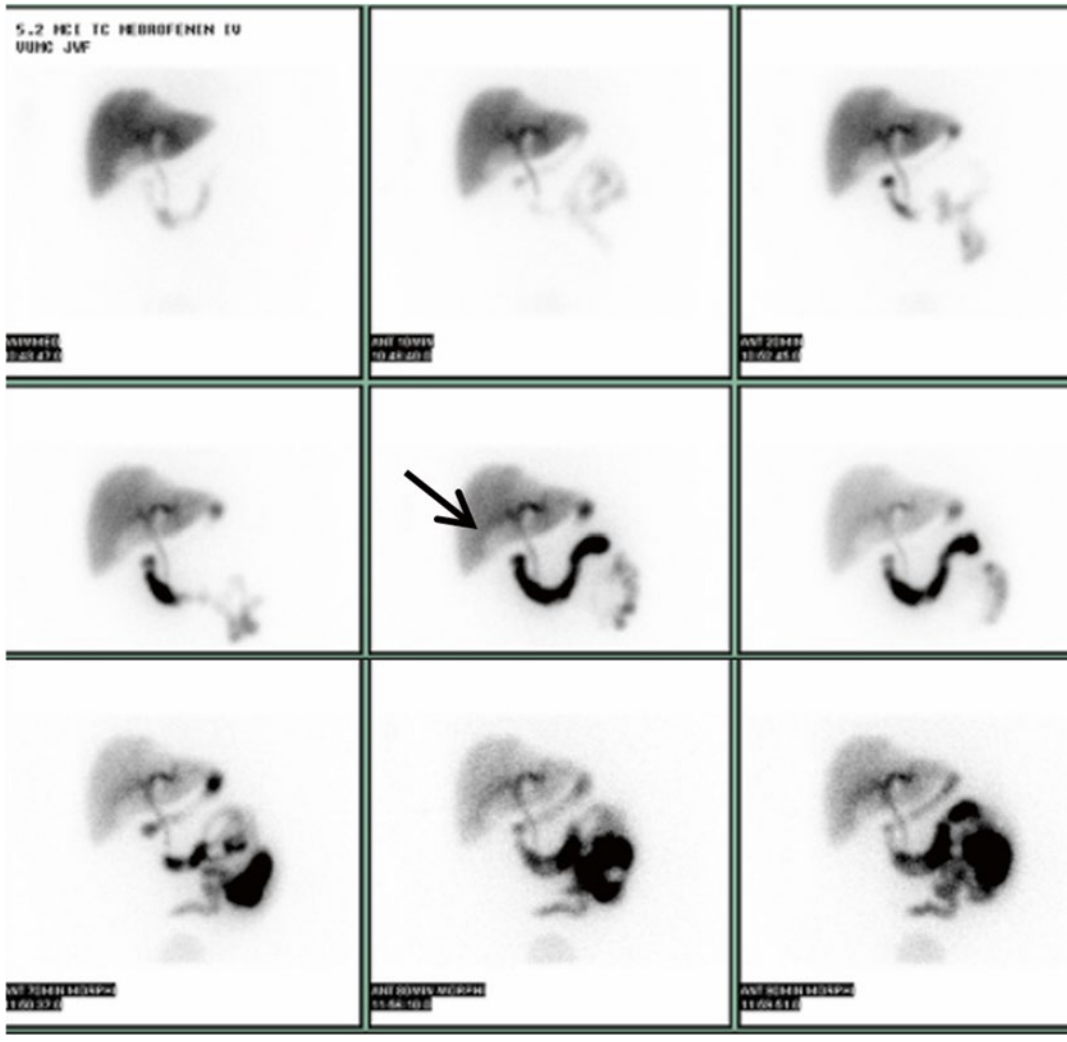

Fig. 3.6 Scintigraphy of patient with acalculous cholecystitis. Gallbladder does not fill at any point during the study. First six images are early images showing contrast transiting from the liver into the duodenum. The last three images are delayed images after the administration of low-dose morphine and show continued passage of contrast into the small bowel without filling the gallbladder. A rim sign (*black arrow*) is visible on multiple images in this series suggesting the possibility of advanced gallbladder disease

required to stabilize a critically ill patient and the catabolism of serum and body proteins may contribute to global body edema and ascites. Thus, the presence of gallbladder wall edema and pericholecystic fluid may not have diagnostic significance. The presence of a sonographic Murphy's sign is quite helpful in establishing the diagnosis but sedation, narcotics, incisional pain, and progression to gallbladder wall necrosis may all confound its detection or limit its presence. While an HIDA scan may be used to exclude acalculous cholecystitis, hepatic dysfunction and biliary stasis can limit the uptake and excretion of the radioactive material and thus not adequately image the biliary tree. Additionally, a significantly distended gallbladder may exhibit poor uptake, regardless of the absence of pathology. Thus, in critically ill patients with a distended gallbladder on imaging and without the ability to provide an appropriate clinical exam, percutaneous drainage may be necessary to establish the diagnosis.

Summary

Diagnosis of acute cholecystitis involves clinical, laboratory, and radiographic findings. TG13 guidelines provide a diagnostic algorithm that optimizes specificity and sensitivity in those patients with a history suggestive of possible acute cholecystitis. Physical exam and laboratory findings should suggest acute inflammatory processes. Imaging should start with RUQ ultrasound and include HIDA if inconclusive. For patients with atypical symptoms, CT may be a better initial imaging modality. The role of MRI is less clear, but may become more important as radiation exposure concerns grow. In select patient populations and certain clinical settings, diagnosis may be difficult or delayed. A high index of suspicion and an attentive approach in at-risk populations is required to limit delays in diagnosis and possible complications.

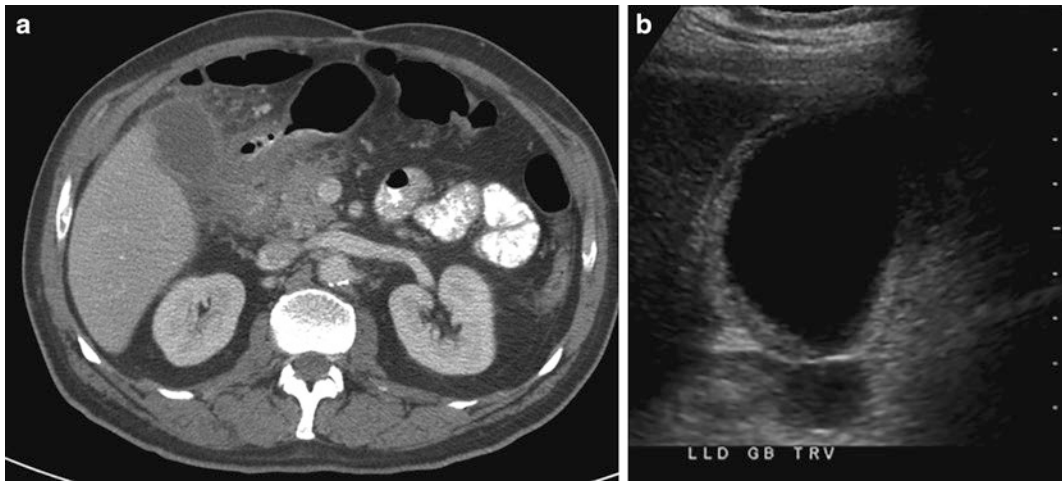

Fig. 3.7 Acalculous cholecystitis. CT demonstrates wall thickening and irregular enhancement of gallbladder. US shows wall thickening but no gallstones are seen

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