Improving Diagnosis of Acute Cholecystitis with US: New Paradigms

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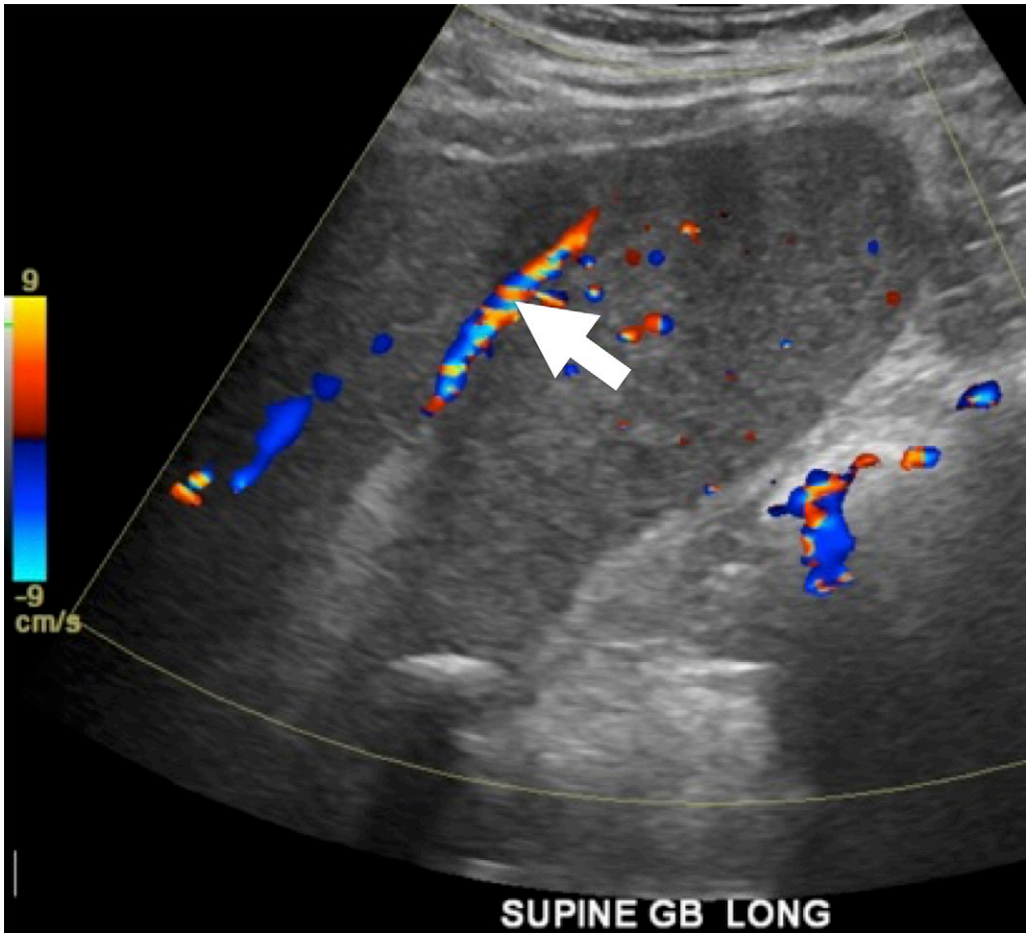

Acute cholecystitis is an inflammatory condition of the gallbladder typically incited by mechanical obstruction. Accurate diagnosis of this common clinical condition is challenging due to variable imaging appearances as well as overlapping clinical manifestations with biliary colic, acute hepatitis, pancreatitis, and cholangiopathies. In acute cholecystitis, increased dilatation and high intraluminal pressures lead to gallbladder inflammation and may progress to gangrenous changes, focal wall necrosis, and subsequent perforation. In acute calculous cholecystitis, gallstones are the cause of obstruction and are often impacted in the gallbladder neck or cystic duct, leading to gallbladder inflammation. In acalculous cholecystitis, patients are typically critically ill, often with hypotensive episodes and prolonged gallbladder stasis, which lead to obstruction, gallbladder ischemia, and inflammation. Helpful sonographic findings of acute cholecystitis include a dilated gallbladder; increased intraluminal pressures in the gallbladder, resulting in a bulging fundus (tensile fundus sign); intraluminal sludge in the setting of right upper quadrant pain; wall hyperemia, which may be quantified by elevated cystic artery velocities or hepatic artery velocities; mucosal ischemic changes, characterized by loss of mucosal echogenicity; pericholecystic inflammation, characterized by hyperechoic pericholecystic fat; and mucosal discontinuity. Extruded complex fluid next to a wall defect is definitive for gallbladder wall perforation, and further evaluation with CT or MRI allows evaluation of the full extent of perforation and other potential complications. The sonographic Murphy sign, while helpful if positive, is relatively insensitive for accurate diagnosis of acute cholecystitis. Thus, overreliance on the sonographic Murphy sign results in surprisingly low diagnostic accuracy in practice.

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Abbreviations: CEUS = contrast-enhanced US, RUQ = right upper quadrant

TEACHING POINTS

- While the sonographic Murphy sign is helpful, studies have shown that it is not sensitive enough to allow accurate diagnosis of acute cholecystitis in many patients.
- More predictive sonographic findings of acute cholecystitis include gallbladder dilatation with a tensile fundus, wall hyperemia with elevated cystic artery velocities, unexplained gallbladder sludge, loss of mucosal sonoreflectivity, mucosal discontinuity, and echogenic pericholecystic fat.
- Understanding the pathophysiology of acute cholecystitis and the progression of gallbladder inflammation is useful in recognizing nuanced imaging findings that can improve image-based diagnostic accuracy.
- Both calculous and acalculous cholecystitis have similar imaging and pathologic findings, with the exception of gallstones being required for acute calculous cholecystitis.
- If the gallbladder is normal in appearance and nondistended (ie, ≤2.2 cm in diameter), acute cholecystitis can be confidently excluded.

Introduction

Acute cholecystitis is a common clinical condition, estimated to occur in greater than 200 000 people per year in the United States (1). Accurate preoperative imaging diagnosis of acute cholecystitis remains challenging due to the variable appearance of acute cholecystitis, especially in early stages.

Abdominal pain caused by gallstones is known as biliary colic. In biliary colic, transient or incomplete obstruction of the cystic duct induces spasms and visceral pain, often occurring postprandially. Biliary colic typically resolves in 4–6 hours (2).

In contrast, acute cholecystitis occurs when there is acute inflammation of an obstructed gallbladder (Fig 1). Gallstones are the inciting cause in 90%–95% of patients with acute cholecystitis, termed acute *calculous* cholecystitis (1). The remaining cases of acute *acalculous* cholecystitis typically occur in critically ill patients with bouts of hypotension and extended periods of gallbladder stasis due to prolonged fasting or total parenteral nutrition, during which the gallbladder does not contract. Lack of periodic emptying of the gallbladder leads to accumulation of viscous bile and mucus, which in turn obstruct the cystic duct, leading to inflammation (1,3).

Many generations of radiologists were taught that the diagnosis of acute cholecystitis hinges on the presence of two concurrent findings: a positive sonographic Murphy sign and gallstones (4). While the sonographic Murphy sign is helpful, studies have shown that it is not sensitive enough to allow accurate diagnosis of acute cholecystitis in many patients (5). Radiologists would miss approximately 52%–76% of patients with acute cholecystitis if only these two findings are used in sonographic diagnosis (1,5,6). Although gallbladder wall thickening and pericholecystic fluid are often cited as additional helpful findings, these may be seen in myriad other entities and conversely are not always seen in acute cholecystitis (7).

More predictive sonographic findings of acute cholecystitis include gallbladder dilatation with a tensile fundus, wall hyperemia with elevated cystic artery velocities, unexplained gallbladder sludge, loss of mucosal sonoreflectivity, mucosal discontinuity, and echogenic pericholecystic fat (8–11). Appropriate identification of these findings may help diagnose acute calculous cholecystitis more confidently, thereby avoiding potential delays in patient care or unnecessary confirmatory testing.

Pathophysiology

Understanding the pathophysiology of acute cholecystitis and the progression of gallbladder inflammation is useful in recognizing nuanced imaging findings that can improve image-based diagnostic accuracy. Acute cholecystitis occurs when increased intraluminal pressure induces mucosal phospholipases to hydrolyze lecithins to toxic lysolecithins, which disrupt the glycoprotein mucus layer of the gallbladder inner wall. The disruption of the protective mucus layer allows bile to directly irritate the mucosal epithelium by detergent action, leading to further inflammation and damage. Simultaneously, the high intraluminal pressure compromises mucosal blood flow. Thus, the double insult to the gallbladder wall with mucosal inflammation and mucosal ischemia results in acute cholecystitis (3). Both calculous and acalculous cholecystitis have similar imaging and pathologic findings, with the exception of gallstones being required for acute calculous cholecystitis (3).

Early acute cholecystitis may not be associated with fever or leukocytosis. As gallbladder inflammation progresses, patients may become febrile and generate inflammatory biomarkers (12). However, acute cholecystitis typically occurs in the absence of bacterial superinfection. Thus, aspirated bile and blood cultures are not typically positive for bacteria (3). As cholecystitis progresses, complications such as gangrene, perforation, or bacterial contamination may follow (13).

At gross pathologic analysis, acute cholecystitis appears as an enlarged and edematous gallbladder, which may have a fibrinopurulent or erythematous surface (Fig 2). Later features include hemorrhage, inflammatory exudates, frank necrosis, or perforation. At histologic analysis, acute cholecystitis is diagnosed when necrosis and acute inflammation (neutrophils) are identified. Necrosis and acute inflammation initially involve only the mucosal surface before progressing to the entire full thickness of the gallbladder wall in later stages (Fig 3). Gangrenous (or necrotizing) cholecystitis is the more severe and late-stage form of acute cholecystitis and shows extensive full-thickness necrosis with acute inflammation (14).

Chronic cholecystitis is an entity distinct from acute cholecystitis that results from chronic wall irritation by gallstones. At pathologic analysis, chronic cholecystitis may display wall thickening with fibrosis and is often associated with Rokitansky-Aschoff sinuses. There is typically a layer of uniform-thickness fibrosis and mild inflammatory lymphocytic infiltration just beneath the lamina propria. Infiltration of inflammatory lymphocytes of the mucosa is minimal, if present (2).

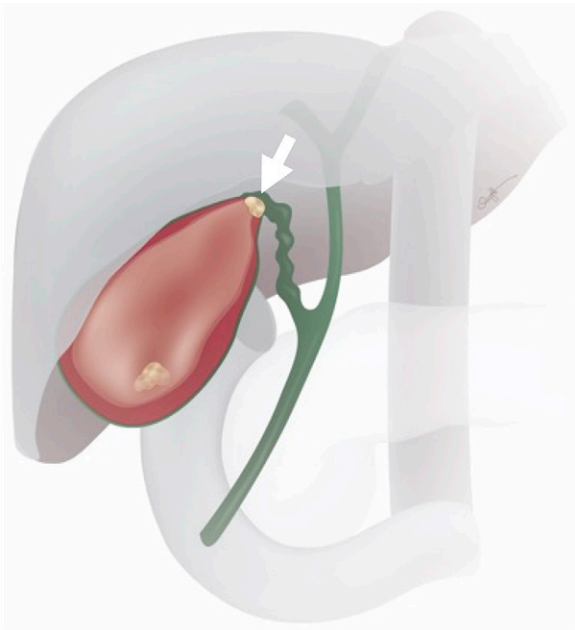

Figure 1. Schematic of acute cholecystitis. In acute calculous cholecystitis, a gallstone (arrow) typically lodges in the neck or cystic duct of the gallbladder, leading to luminal obstruction, distention, and gallbladder wall inflammation. (Courtesy of Amy Thomas, Stanford University.)

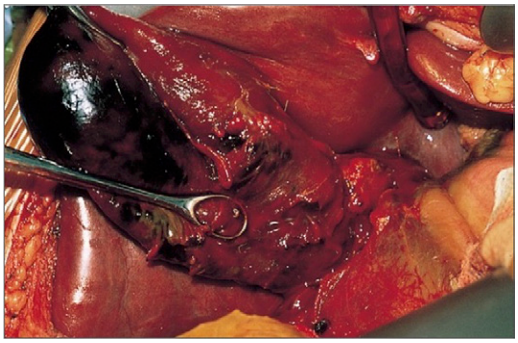

Figure 2. In vivo photograph shows acute gangrenous cholecystitis. The gallbladder (grasped by the tenaculum) is swollen with a deep purple to black serosa. (Courtesy of David A. Spain, MD, Stanford Hospital.)

Emphysematous cholecystitis, xanthogranulomatous cholecystitis, and hemorrhagic cholecystitis are rare variations of acute cholecystitis, which are beyond the scope of this discussion.

Clinical Criteria for Acute Cholecystitis

The 2018 Tokyo Guidelines are a widely implemented and referenced standard used to clinically diagnose and grade acute cholecystitis before surgery (15). The Tokyo Guidelines use three principal criteria for diagnosis of acute cholecystitis: *(a)* physical examination findings of right upper quadrant (RUQ) inflammation (clinical Murphy sign, RUQ pain or mass), *(b)* biochemical signs of systemic inflammation (fever, leukocytosis, elevated C-reactive protein level), and *(c)* imaging findings diagnostic of acute cholecystitis. The combination of physical examination findings and biochemical evidence of inflammation is categorized as suspicious for acute cholecystitis. However, the addition of positive imaging findings is categorized as definite for the diagnosis of acute cholecystitis (15).

Despite an emphasis on imaging, the Tokyo Guidelines provide scant detail regarding image-based diagnosis. Definitions for gallbladder wall thickening (>4 mm) and a dilated gallbladder (≥8 cm long or ≥4 cm transversely) are provided. Gallstones or debris and pericholecystic fluid are described as frequent imaging findings associated with acute cholecystitis. However, these findings alone are typically insufficient for accurate diagnosis despite the Tokyo Guidelines' pivotal emphasis on imaging.

Imaging Options

For imaging diagnosis of acute cholecystitis, US is the first-line imaging modality recommended by the Tokyo Guidelines, the 2020 World Society of Emergency Surgery guidelines, and the American College of Radiology appropriateness guidelines (1,15–17), with reported high sensitivity (81%) and specificity (80%) in a meta-analysis (18). US can be performed expediently at the bedside and does not require intravenous contrast material or ionizing radiation. If the gallbladder is normal in appearance and nondistended (ie, ≤2.2 cm in diameter), acute cholecystitis can be confidently excluded (19). The exception to this is if the gallbladder is perforated.

For patients with complicated cholecystitis, CT or MRI allows identification and characterization of perforations or extraluminal collections. If choledocholithiasis is suspected, MR cholangiopancreatography is the imaging modality of choice (20,21). In patients in whom the diagnosis is equivocal after initial US, then CT, hepatobiliary scintigraphy (also commonly referred to as cholescintigraphy or hepatobiliary iminodiacetic acid [HIDA] scanning), or repeat US within 12–24 hours may be helpful. With biliary colic, symptoms typically resolve in 6–12 hours. However, in acute cholecystitis, the gallbladder's appearance often changes dramatically over time, which can be easily appreciated with repeat US. In patients in whom repeat US in 12–24 hours is not feasible, further evaluation with hepatobiliary scintigraphy or CT may be useful (1).

With hepatobiliary scintigraphy, technetium-labeled analogue iminodiacetic acid (radiotracer) is injected intravenously in a fasting patient. Morphine is often administrated to cause sphincter of Oddi contraction, diverting bile into the gallbladder (1,22). If the gallbladder fills with radiotracer after 30–60 minutes, the cystic duct is confirmed to be patent and acute cholecystitis can be excluded. Conversely, a nonvisualized gallbladder is presumed to represent acute cholecystitis (1,22). Sensitivity and specificity are high (>90%). However, hepatobiliary scintigraphy is expensive and time-consuming, exposes patients to ionizing radiation, and is not always readily available (18). Consequently, repeat US in 12–24 hours or CT has largely supplanted hepatobiliary scintigraphy in evaluation of equivocal cases at our institution.

Contrast-enhanced US (CEUS) allows assessment of gallbladder wall integrity, especially in patients with renal dysfunction, for whom contrast-enhanced CT or MRI may not

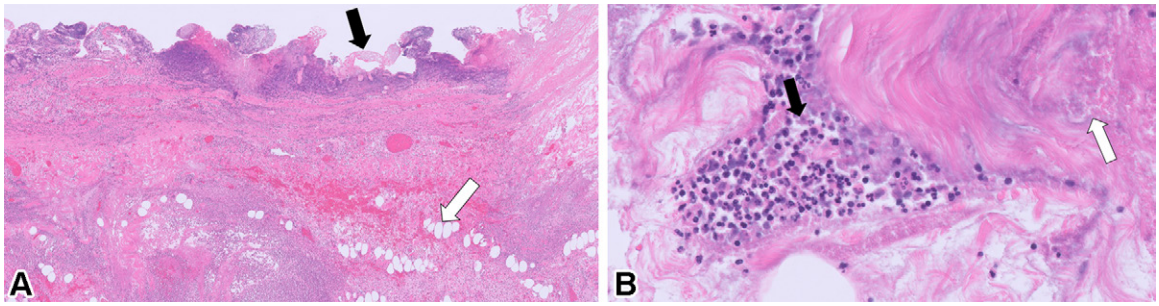

Figure 3. Histopathologic examples of acute gangrenous cholecystitis. **(A)** Low-power photomicrograph of a gallbladder with acute (gangrenous) cholecystitis shows full-thickness ischemic changes, with obliteration of the mucosa (black arrow) and liquefactive necrosis of the wall (white arrow). (Hematoxylin-eosin stain; original magnification, ×40.) **(B)** High-power photomicrograph of the same histologic section shows abundant neutrophils (black arrow) surrounded by necrotic debris (white arrow). (Hematoxylin-eosin stain; original magnification, ×400.)

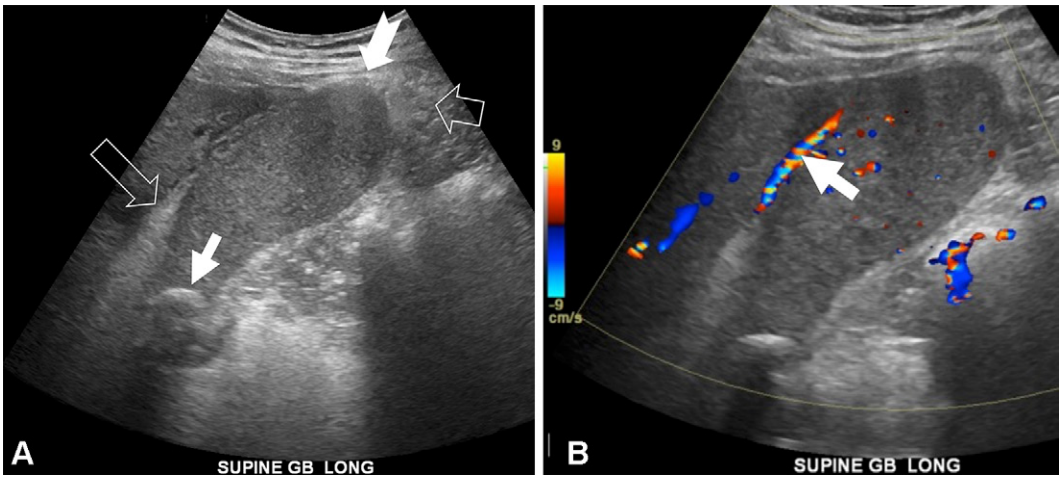

Figure 4. Acute cholecystitis in a 63-year-old man. **(A)** Gray-scale longitudinal US image of the gallbladder shows a thin gallbladder wall without pericholecystic fluid. However, other findings suggestive of acute cholecystitis are seen, including marked gallbladder luminal dilatation to 11.5 × 4.2 cm (measurements not shown), a subtle tensile fundus sign (thick solid arrow), echogenic pericholecystic fat adjacent to the gallbladder fundus (short open arrow) and in the triangle of Calot (long open arrow), intraluminal sludge, and a lodged gallstone (thin solid arrow) at the gallbladder neck. **(B)** Color Doppler US image of the gallbladder shows moderate hyperemia of the cystic artery (arrow).

be an option. CEUS is also useful in evaluation of gallbladder wall perfusion (23). A normal gallbladder wall enhances homogeneously, whereas an inflamed and thus hyperemic gallbladder wall perfuses earlier than adjacent liver. Irregularity or nonperfusion of the gallbladder wall at CEUS suggests mucosal ulceration and potentially perforation (23).

Sonographic Features of Acute Cholecystitis: New Paradigms

Gallbladder Dilatation and Tensile Fundus Sign

Acute cholecystitis typically begins with gallbladder outlet obstruction leading to gallbladder dilatation (8,19,24). Shaish et al (19) showed that a gallbladder width (transverse diameter) less than 2.2 cm correlates with nondistention and allows confident exclusion of acute cholecystitis in the absence of gallbladder perforation. For gallbladder dilatation, the Tokyo Guidelines use 4 × 8 cm (transverse × longitudinal) as an approximate threshold. Most patients with acute cholecystitis have a gallbladder that exceeds one or both of these dimensions (15).

However, image-based evidence of increased intraluminal pressure (Fig 4) is more predictive of pathologic gallbladder dilatation than is absolute gallbladder size. When the gallbladder bulges the anterior abdominal wall outward, this is an excellent indicator of high intraluminal pressures. This occurs when the intraluminal pressure of the gallbladder exceeds the ability of the anterior abdominal wall to flatten the gallbladder fundus, termed the *tensile fundus sign* (8). This sign was shown to be sensitive (74%) and highly specific (96%) for acute cholecystitis in patients with RUQ pain by An et al (8) (Fig 5).

At US, this finding is best appreciated when using a high-resolution or high-frequency linear transducer directly over the fundus of the gallbladder (25). Care should be taken not to exert too much direct pressure with the transducer, as this can inadvertently flatten the gallbladder and obscure this finding. Potential pitfalls of this sign include noncontact with the anterior abdominal wall, a decompressed gallbladder

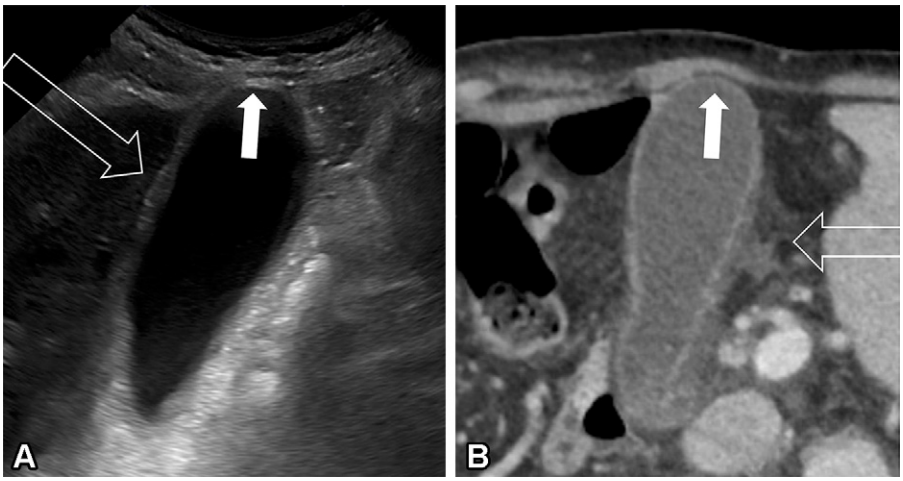

Figure 5. Acute cholecystitis in a 76-year-old man. **(A)** Gray-scale US image of the right upper quadrant (RUQ) shows the dilated gallbladder exerting mass effect on the anterior abdominal wall, bulging it outward (the tensile fundus sign) (solid arrow) so that it resists the transducer during assessment of the sonographic Murphy sign, with some area of wall thickening (open arrow). **(B)** Axial image from contrast-enhanced CT performed 2 hours before the US study shows the tensile fundus sign (solid arrow) and pericholecystic fat stranding (open arrow). While the gallbladder wall is mostly edematous, the area of contact with the abdominal wall is relatively thin.

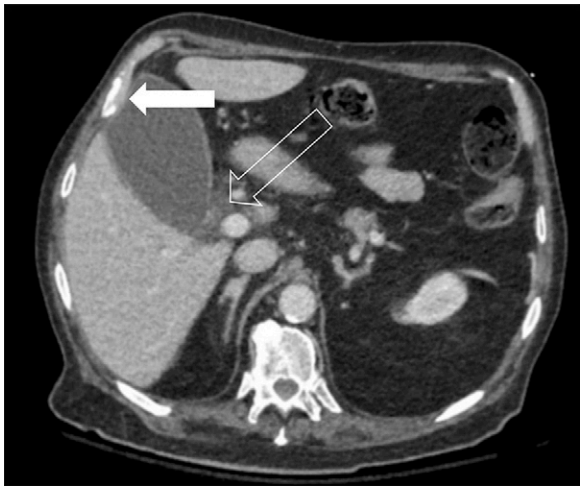

Figure 6. Pathologically proven acute cholecystitis in an 81-year old man. Axial contrast-enhanced CT image shows a gallbladder distended to 11 × 6 cm (measurements not shown); however, fundal mass effect on the anterior abdominal wall is not seen due to an adjacent rib (solid arrow), which prevents the gallbladder from pushing the abdominal wall outward. Note the lack of wall thickening or hyperattenuating gallstones but the presence of only mild pericholecystic stranding (open arrow) near the gallbladder neck, suggesting acute cholecystitis.

secondary to perforation in the setting of advanced cholecystitis, or a gallbladder fundus immediately deep to a rib that prevents deformation of the anterior abdominal wall (Fig 6).

Gallbladder Sludge

Gallbladder sludge (or biliary precipitate) is defined as layering inspissated material in the gallbladder without associated shadowing (26). Biliary sludge is composed of mucus, precipitated cholesterol, and calcium salts and indicates some degree of bile stasis in the gallbladder, most commonly seen in patients undergoing prolonged fasting (ie, intensive care unit [ICU] patients, postoperative patients, or patients receiving total parenteral nutrition). Prolonged fasting prevents periodic gallbladder emptying; thus, fresh bile cannot replenish in the gallbladder, leading to sludge formation.

An exception to this is pregnancy, in which sludge formation may be increased due to hormonal changes (1). Otherwise, in an outpatient setting, the incidence of gallbladder sludge is exceedingly low (27). Thus, if a previously healthy patient with acute RUQ pain has intraluminal sludge, gallbladder dysfunction may be suspected (Fig 4).

Gallstones

The prevalence of gallstones is increasing, affecting 10%–15% of adults in Western populations. Risk factors for gallstones include obesity, diabetes, and metabolic syndrome (28,29). Crohn disease, cirrhosis, or medications (octreotide, thiazides) are additional risk factors for gallstones (28). Most gallstones are cholesterol stones, which form when the concentration of cholesterol exceeds the solubilizing capacity of bile and precipitates out of solution. Free cholesterol is toxic to the gallbladder, leading to hypomotility and hypersecretion of mucus, which promote stone formation (30).

Despite the increasing prevalence of gallstones, most patients with gallstones are asymptomatic (28). Although acute calculous cholecystitis is the most common gallstone-related complication, less than 10% of patients with gallstones develop acute cholecystitis (29,31). Further, biliary colic caused by gallstones may transiently mimic acute cholecystitis. Thus, the presence of gallstones alone is not predictive of acute cholecystitis (12).

However, if a stone is seen in the neck or cystic duct of the gallbladder, this is a more suspicious finding (Fig 4). In these patients, supine and lateral decubitus views may help determine if the stone is mobile or if it is lodged or impacted in the gallbladder neck or cystic duct. Notably, a gallstone in the cystic duct may be difficult to sonographically visualize due to the distance from the central gallbladder lumen and the potential for bowel gas to obscure the stone itself or its posterior acoustic shadow (Fig 4).

Wall Hyperemia: Elevated Hepatic Artery and Cystic Artery Velocities

Acute gallbladder inflammation typically results in increased blood flow. Subjectively, this may be appreciated as wall hyperemia at color or power Doppler US as well as more recent

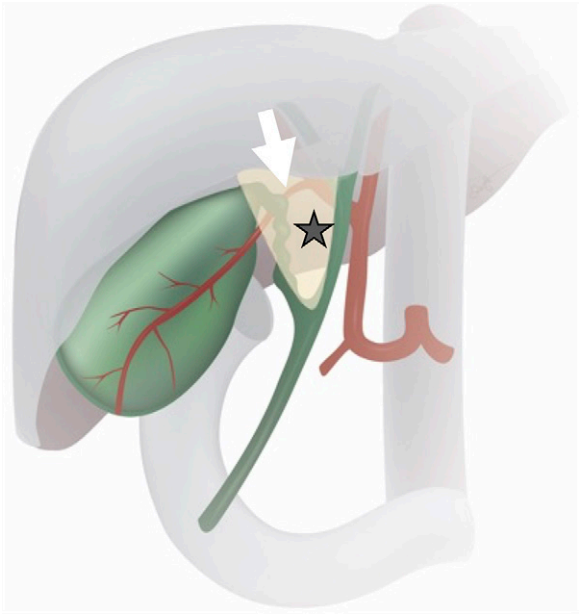

Figure 7. Hepatic artery and cystic artery anatomy. The common hepatic artery usually arises from the celiac artery. After the takeoff of the gastroduodenal artery, the common hepatic artery becomes the proper hepatic artery. This in turn bifurcates into the right and left hepatic arteries. The cystic artery (arrow) arises from the right hepatic artery to perfuse the gallbladder. The triangle of Calot (★) is demarcated by the liver, cystic duct, and common hepatic duct. In the setting of acute cholecystitis, fat in this area as well as fat adjacent to other parts of the gallbladder may become echogenic due to inflammation. (Courtesy of Amy Thomas, Stanford University.)

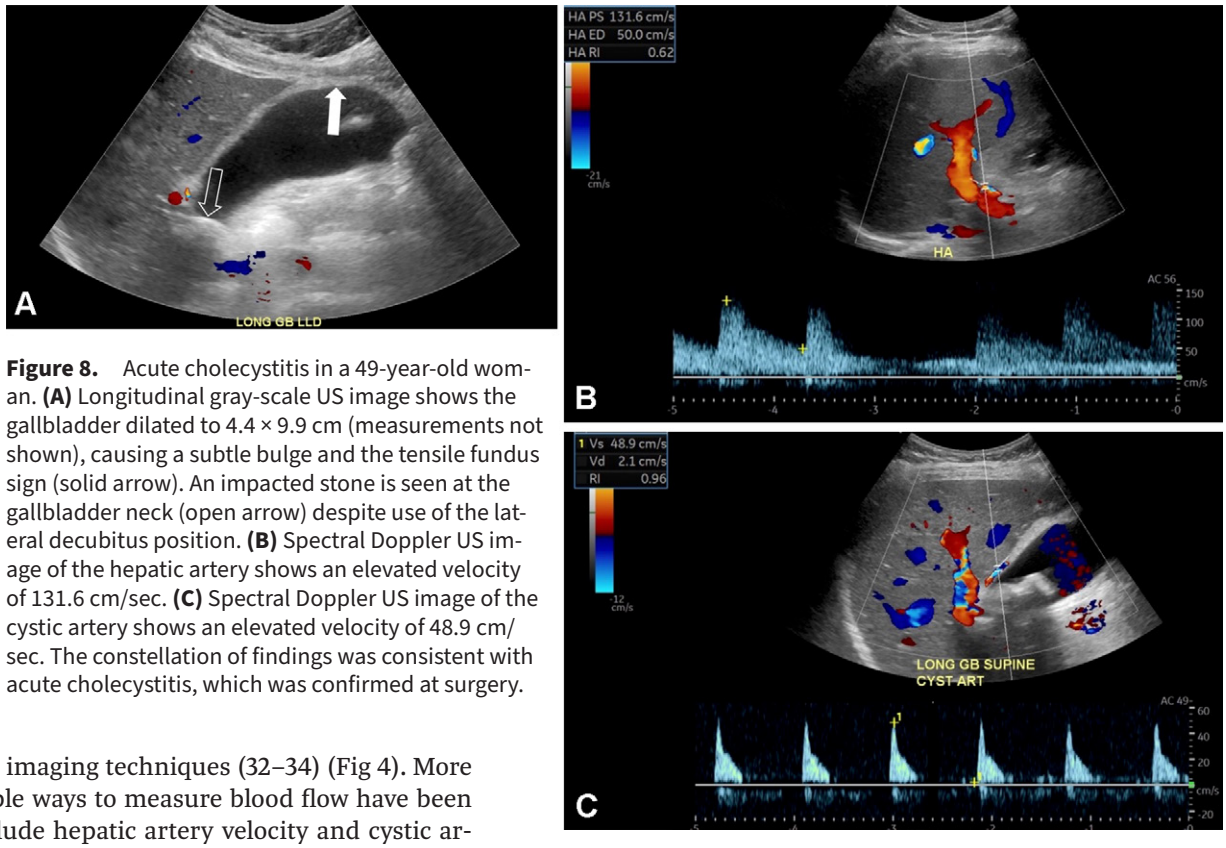

Figure 8. Acute cholecystitis in a 49-year-old woman. **(A)** Longitudinal gray-scale US image shows the gallbladder dilated to 4.4 × 9.9 cm (measurements not shown), causing a subtle bulge and the tensile fundus sign (solid arrow). An impacted stone is seen at the gallbladder neck (open arrow) despite use of the lateral decubitus position. **(B)** Spectral Doppler US image of the hepatic artery shows an elevated velocity of 131.6 cm/sec. **(C)** Spectral Doppler US image of the cystic artery shows an elevated velocity of 48.9 cm/sec. The constellation of findings was consistent with acute cholecystitis, which was confirmed at surgery.

microvascular flow imaging techniques (32–34) (Fig 4). More recently, quantifiable ways to measure blood flow have been studied, which include hepatic artery velocity and cystic artery velocity (9,35).

The anatomy of the hepatic artery and cystic artery is shown in Figure 7. The hepatic artery velocity should be sampled as it travels parallel to the main portal vein. Peak systolic hepatic artery velocity greater than or equal to 100 cm/sec is 2 SDs above the mean (35). In the setting of RUQ pain, an elevated hepatic artery velocity has been shown to be statistically significantly correlated with acute cholecystitis and more accurate in predicting acute cholecystitis than either gallstones or the sonographic Murphy sign (35). However, because the hepatic artery perfuses both the gallbladder and the liver, liver diseases such as cirrhosis, acute alcoholic hepatitis, and liver metastases may also increase the hepatic artery velocity, rendering this finding less useful for acute cholecystitis (6) (Fig 8).

More recently, Perez et al (9) found that an elevated cystic artery velocity is a more reliable marker of gallbladder hyperemia. The cystic artery is the only arterial blood supply to the gallbladder. Therefore, alterations in gallbladder perfusion are more directly reflected in the cystic artery, with less potential for influence from primary hepatic processes. The

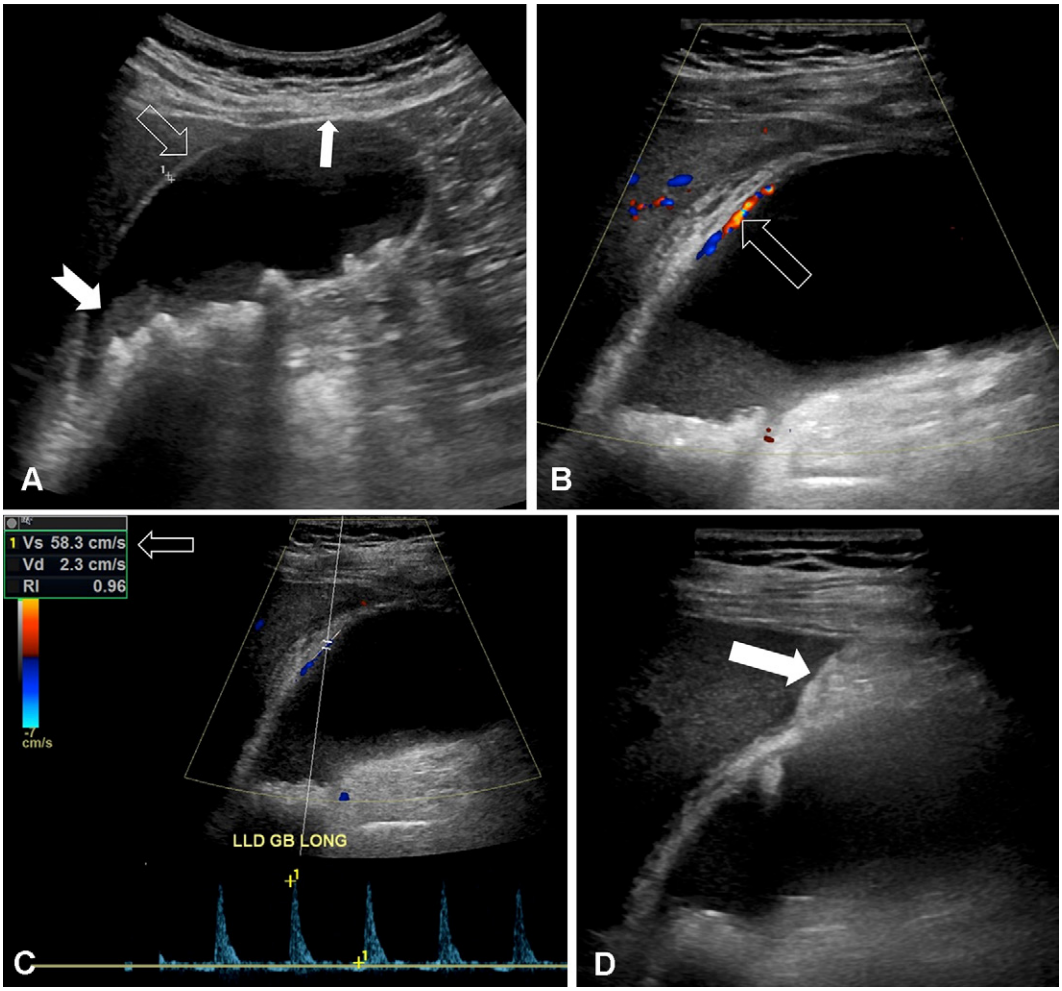

Figure 9. Gangrenous cholecystitis in a 67-year old man with progression in imaging appearance over 2 days. **(A)** Gray-scale longitudinal US image shows a dilated gallbladder with layering sludge and shadowing stones (thick solid arrow). Although the wall is not thickened (open arrow), the gallbladder subtly deforms the contour of the anterior abdominal wall (thin solid arrow). **(B)** Image from repeat US 2 days later shows significant change in the gallbladder, including a striated thickened wall with hypervascularity (arrow). **(C)** Spectral US image of this area shows an elevated cystic artery velocity of 58 cm/sec (arrow). **(D)** US image shows that hyperechoic pericholecystic fat consistent with transmural inflammation (arrow) is more evident.

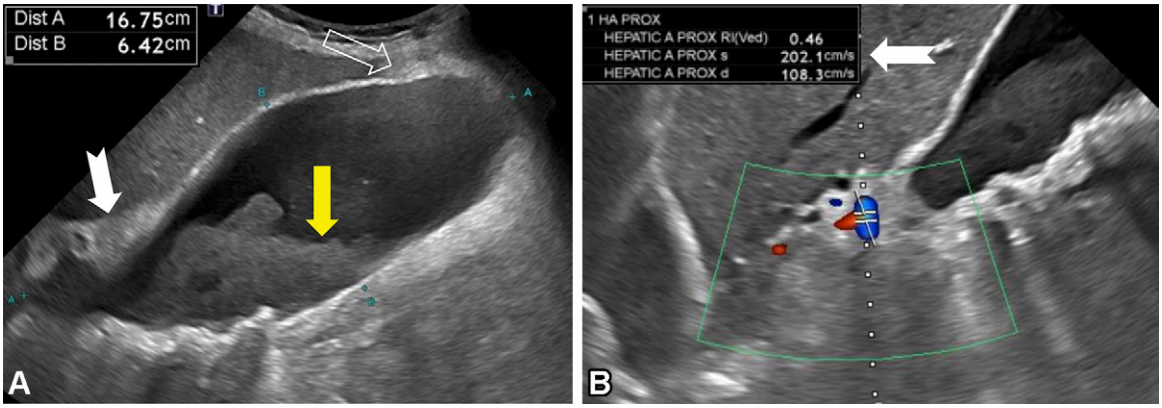

Figure 10. Acute cholecystitis in a 79-year-old man in septic shock. **(A)** Gray-scale longitudinal US image shows the gallbladder markedly distended to 16.7 × 6.4 cm, with sludge (yellow arrow) and echogenic pericholecystic fat along the gallbladder fundus (open arrow) and triangle of Calot (white arrow). **(B)** Color Doppler US image shows an elevated hepatic artery velocity of 202 cm/sec (arrow).

cystic artery is best visualized parallel to the long axis of the gallbladder, through a right lateral acoustic window with low pulse repetition frequency at color Doppler US (9). In normal patients, the cystic artery may not always be visualized (9).

Perez et al (9) showed that peak systolic cystic artery velocity greater than or equal to 40 cm/sec can help identify acute cholecystitis with 72% sensitivity, 84% accuracy, and 92% positive predictive value (PPV) (Figs 8, 9). For borderline elevated cystic artery velocities of 30–40 cm/sec, careful evaluation of other sonographic features of acute cholecystitis is warranted, as some cases of acute cholecystitis may not reach the 40-cm/sec threshold (Fig 10). Notably, this finding has been validated only in the setting of patients presenting to the emergency department with RUQ pain (9).

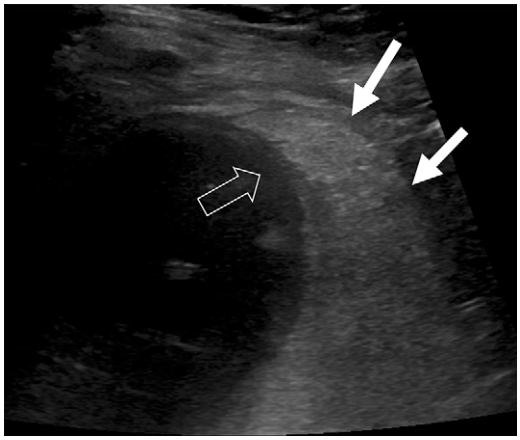

Figure 11. Acute gangrenous cholecystitis in a 75-year-old man. Linear high-resolution gray-scale US image shows marked echogenic pericholecystic fat (solid arrows), consistent with transmural spread of inflammation through the gallbladder wall to involve the adjacent fat. There is associated discontinuity of the fundal mucosa with distinct loss of mucosal sonoreflectivity (open arrow), suggesting gangrenous cholecystitis.

In other clinical contexts or in patients with confounding pathologic conditions, the usefulness of this finding is unclear. Moreover, in patients with gangrenous cholecystitis with compromised blood flow to the gallbladder, the cystic artery velocity may not be as predictive. The resistive index has not been shown to correlate with acute cholecystitis in the hepatic artery and has not been studied in the cystic artery (9,35), to our knowledge.

Echogenic Pericholecystic Fat

As acute cholecystitis progresses, transmural spread of inflammation extends beyond the gallbladder wall to involve the adjacent fat in the omentum or fat in the triangle of Calot (36) (Fig 7). Inflamed fat appears hyperechoic at US compared with the adjacent subcutaneous fat (Figs 9–11) (10,11). Fat deep to the gallbladder typically appears bright secondary to posterior acoustic enhancement from fluid in the gallbladder and should therefore not be used to assess echogenicity. When echogenic pericholecystic fat is present, the likelihood ratio of gangrenous cholecystitis is 4.6 (10). The CT and MRI correlate for fat inflammation is pericholecystic fat stranding or edema, but this is typically a later finding in acute cholecystitis (Fig 6).

Loss of Mucosal Sonoreflectivity

Gangrenous change may be seen in up to 39% of patients with acute calculous cholecystitis (37,38). Risk factors include elderly age and diabetes mellitus (38,39). Gangrenous cholecystitis has many important clinical implications, including higher mortality rates, greater risk of sepsis, more frequent conversion to open cholecystectomy, and greater risk of prolonged hospitalization (1,40–43). Thus, identification of this complication is important to help direct patient treatment and management.

Inflammation and mucosal breakdown of the gallbladder mucosa may appear sonographically as loss of the normal echogenic mucosa. This finding may be especially helpful in the setting of acute cholecystitis in which the gallbladder wall is not only thickened, but the mucosa is no longer distinctly sonoreflective. It is a subtle finding that represents mucosal ischemia and gangrenous cholecystitis, often best appreciated with a linear high-frequency transducer (Fig 12).

As areas of mucosal discontinuity progress, frank perforation may follow (10). Irregular hypoenhancement of gallbladder mucosa is the CT or MRI equivalent of gangrenous change (Fig 13). Rarely, the mucosa may detach from the gallbladder wall, a finding termed *sloughed mucosa*. This is a rare but specific sonographic appearance of gangrenous cholecystitis.

Mucosal Discontinuity and Perforation

Gangrenous cholecystitis may progress to perforation, which in turn can lead to abscess formation, bile peritonitis, or sepsis (39,44). Gallbladder perforation occurs in up to 2%–11% of patients with acute cholecystitis and increases mortality risk (39,44,45). Areas of wall discontinuity may be identified sonographically with adjacent extruded complex extraluminal fluid (Fig 14).

Perforations often occur along the bare area of the gallbladder due to lack of a peritoneal lining in this area but may occur anywhere along the gallbladder wall, including the gallbladder fundus due to its location farthest from the blood supply and its greater wall tension as a function of greater diameter (Laplace's Law: $T = P \cdot R/2$, where T = tension, P = pressure, and R = radius) (39,44). As intraluminal bile continues to extrude out of a perforated gallbladder, the lumen may become decompressed or even crenulated like a deflated balloon. When perforation is suspected at US, CT or CEUS may allow evaluation of the full extent of bile extrusion (37,39) (Fig 15) or help delineate phlegmonous change from gallbladder perforation (Fig 16).

Diagnostic Features: Old Paradigms

Sonographic Murphy Sign

Although the combination of a positive sonographic Murphy sign and gallstones was initially reported (in the early 1980s) to have high diagnostic accuracy for diagnosis of acute cholecystitis (4,46), subsequent studies have failed to corroborate these findings (35,47,48).

The Murphy sign (also known as the surgical Murphy sign or deep-grip palpation) was originally described as inadvertent cessation of breathing by a patient when the examiner hooks their fingers deep under the patient's right costal margin. As the patient deeply inhales, the diaphragm, liver, and gallbladder descend until the gallbladder reaches the examiner's hooked fingers (Fig 17). If the gallbladder is inflamed, this direct contact elicits exquisite pain, and inspiration suddenly stops (49).

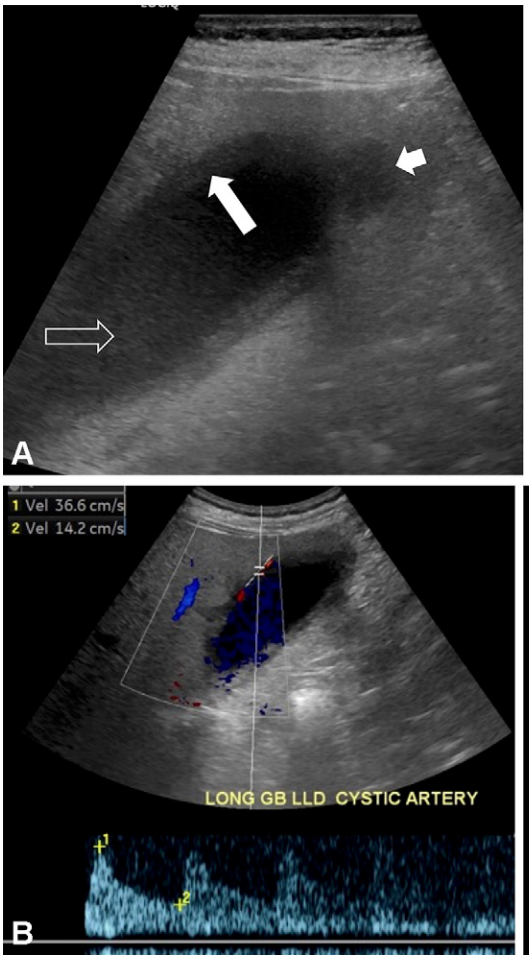

Figure 12. Acute cholecystitis in a 46-year-old man with 3 days of epigastric pain. **(A)** Gray-scale US image of the gallbladder fundus obtained with a linear transducer shows a thickening gallbladder wall with loss of the normally echogenic mucosa in the gallbladder wall (long solid arrow) and the presence of intraluminal sludge (open arrow). Incidental note is made of focal fat sparing in the adjacent liver (short solid arrow). **(B)** Spectral Doppler US image shows that the cystic artery velocity is borderline elevated at 37 cm/sec. **(C)** Coronal image from subsequent contrast-enhanced CT shows subtle reactive hepatic hyperemia surrounding the gallbladder (open arrow) and pericholecystic stranding (solid arrow), the CT equivalent of echogenic pericholecystic fat.

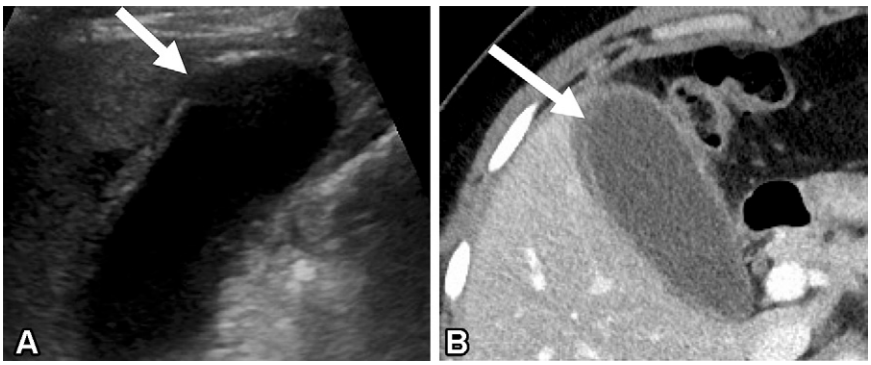

Figure 13. Acute cholecystitis in a 37-year-old man with RUQ pain. **(A)** Gray-scale US image of the gallbladder shows a focal area of loss (arrow) of the normally echogenic mucosa. **(B)** Corresponding contrast-enhanced CT image shows that this same area is relatively hypoenhancing (arrow), consistent with mucosal ischemia.

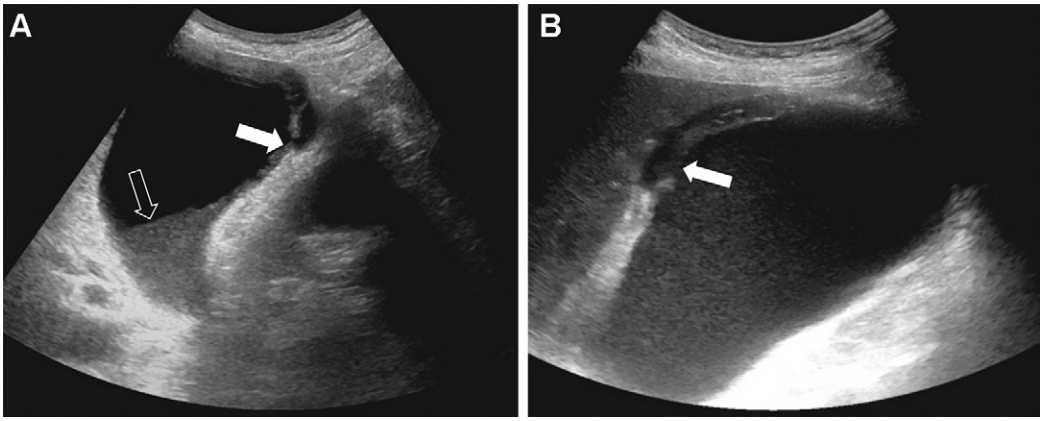

Figure 14. Gangrenous cholecystitis complicated by frank perforation in a 63-year-old man. **(A)** Gray-scale US image of the RUQ in the left lateral decubitus position shows the gallbladder dilated to 12.9 × 6.5 cm (measurements not shown) with layering sludge (open arrow) and a focal area of mucosal discontinuity (solid arrow), with adjacent extraluminal fluid consistent with perforation. **(B)** Longitudinal US image shows an additional site of mucosal discontinuity (arrow), with adjacent extraluminal fluid in the bare area.

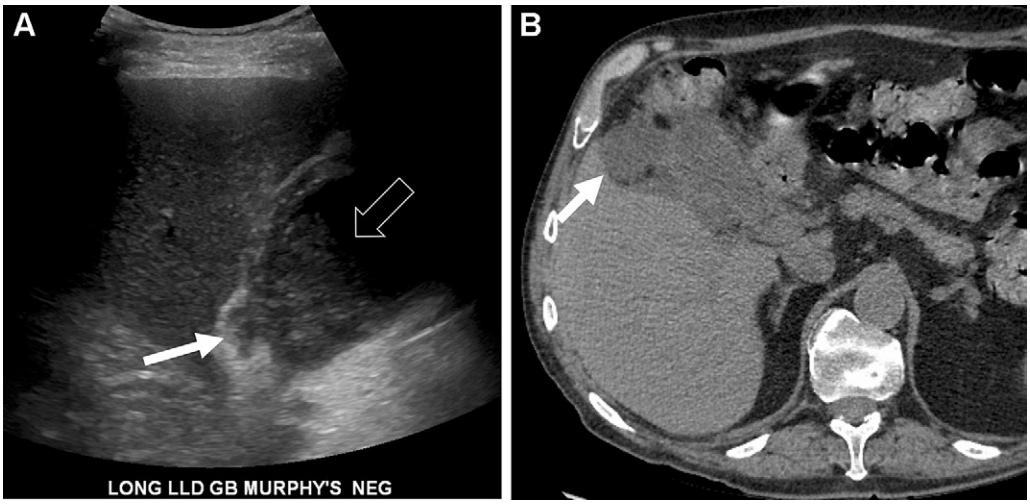

Figure 15. Perforated cholecystitis resulting in progressive decompression of the gallbladder in a 72-year-old man. **(A)** Gray-scale US image shows a focal defect in the gallbladder wall with extrusion of intraluminal contents (solid arrow). There is intraluminal sludge (open arrow). The sonographic Murphy sign was negative in this patient. **(B)** Axial noncontrast CT image obtained several hours later shows further decompression of the gallbladder due to further extrusion of intraluminal contents out of the gallbladder (arrow).

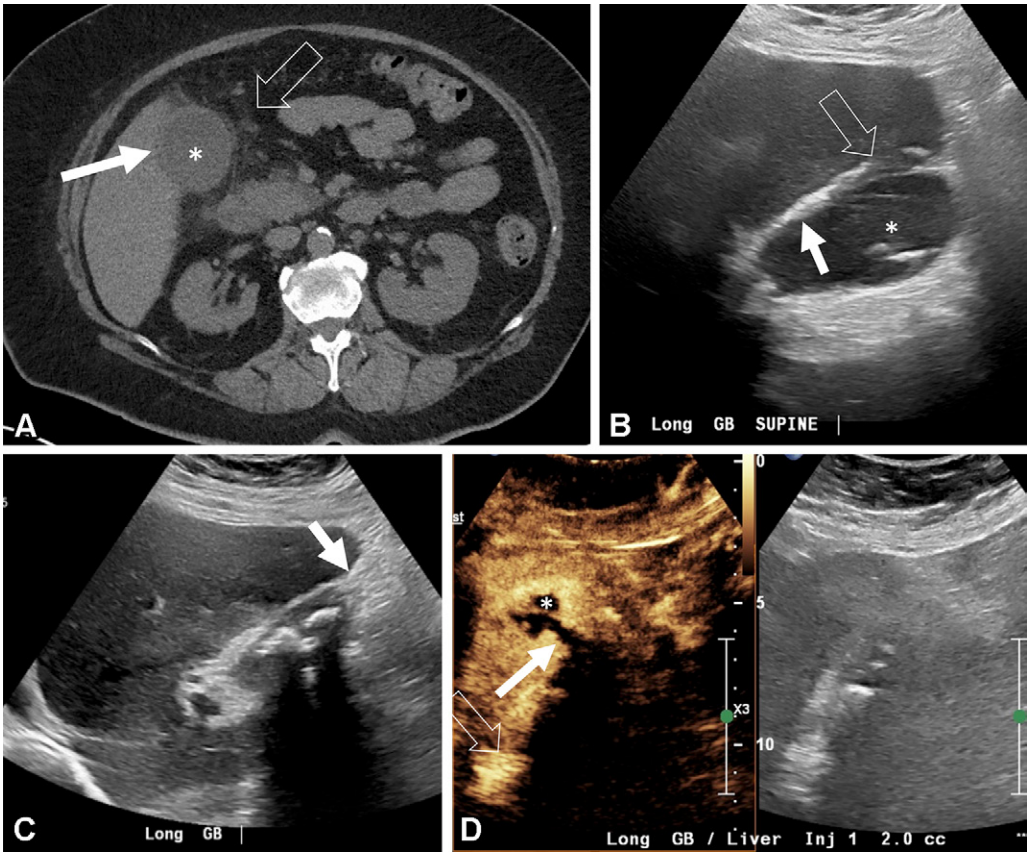

Figure 16. Cholecystitis confirmed with CEUS in a 58-year-old woman with epigastric pain. **(A)** Axial noncontrast CT image shows the gallbladder (*) with wall thickening (solid arrow) and pericholecystic stranding (open arrow). **(B)** Gray-scale US image shows a stone-filled gallbladder (*) that is not overtly dilated with wall thickening (solid arrow) and areas of wall heterogeneity (open arrow). **(C)** US image shows echogenic pericholecystic fat (arrow) adjacent to the gallbladder fundus, suggesting transmural inflammation, a sonographic correlate for the pericholecystic stranding seen at CT. **(D)** CEUS (left) and gray-scale (right) US images show a frank defect (solid arrow) in the gallbladder wall, a small intrahepatic abscess (*), and pericholecystic hyperemia (open arrow). (Case courtesy of Razan Noorelahi, MD, and David Fetzer, MD, University of Texas Southwestern.)

The sonographic Murphy sign is an extrapolation of the Murphy sign. It is considered positive if the point of maximal tenderness corresponds to the gallbladder, as localized by the US probe directly over the gallbladder (4) (Fig 18). Because one cannot "hook" a transducer under the costal margin in the same way as an examiner's fingers, cessation of breathing is not required.

The accuracy of the sonographic Murphy sign is limited for several reasons. First, the sign has poor sensitivity. In a study by Simeone et al (5), only 33% of patients with acute cholecystitis had a sonographic Murphy sign. Other studies have similarly found the sonographic Murphy sign to be poorly predictive of acute cholecystitis (35,47,48).

Second, this sign may be falsely negative or the pain poorly localized in patients treated with analgesic medications, in elderly or diabetic patients who have blunted pain perception, in patients with gangrenous cholecystitis in which the gallbladder is denervated, or in patients with perforated cholecystitis in which the gallbladder is no longer markedly distended (6,35). Thus, a negative sonographic Murphy sign does not exclude acute cholecystitis.

Third, this sign may be falsely positive due to inflammation in surrounding structures such as the liver, pancreas, stomach, or duodenum (47). Finally, the sign is operator dependent and therefore subject to variability and subjectivity. Thus, overreliance on the sonographic Murphy sign is discouraged.

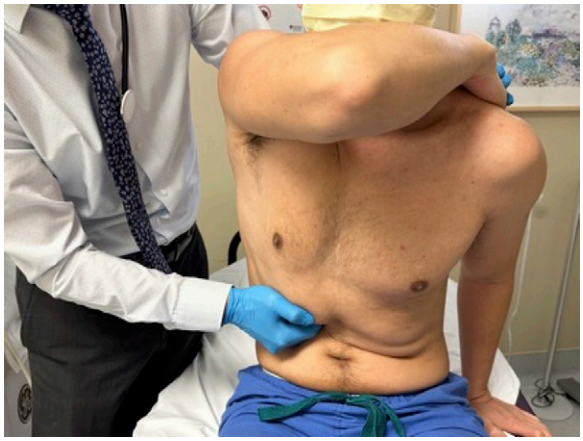

Figure 17. Murphy sign. John B. Murphy (1857–1916) described this clinical examination sign for diagnosing acute cholecystitis. A sitting patient is examined from behind with the examiner's fingers gripped under the right costal margin. Deep inspiration causes the gallbladder to descend and abut the examiner's fingers. If inadvertent cessation of breathing occurs during inspiration, this is considered a positive test.

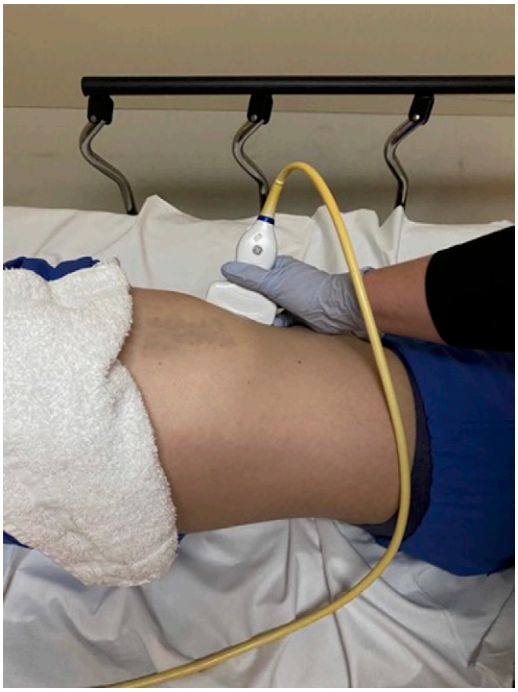

Figure 18. Sonographic Murphy sign. The sonographic Murphy sign is considered positive if the point of maximal tenderness corresponds directly to the gallbladder when the US transducer is positioned directly over the gallbladder. Cessation of breathing is not part of this sign and is not a requirement for a positive result.

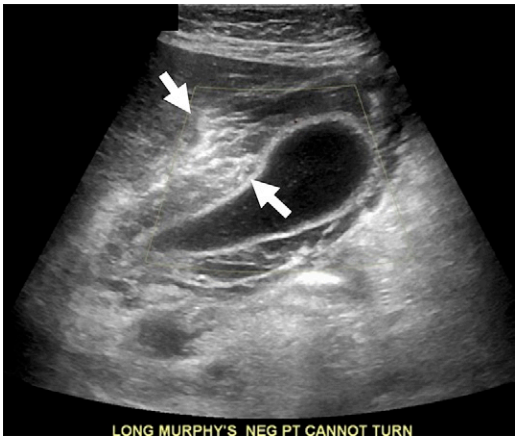

Figure 19. Gallbladder wall thickening due to congestive heart failure in a 57-year-old man. Longitudinal gray-scale US image of the gallbladder shows a thickened wall with an edematous, lamellated, or striated appearance (the entire thickness of the wall is indicated by the arrows). Edema separates the interstices of the gallbladder wall and should not be confused with pericholecystic fluid. There are no additional features of acute calculous cholecystitis. Note the well-defined inner mucosa, which would be atypical for acute cholecystitis.

Gallbladder Wall Thickening

Gallbladder wall thickening (≥4 mm in thickness) is often described as a finding commonly seen with acute cholecystitis (15,50). Measurement of the wall adjacent to the interface with the liver may be less prone to image distortion from adjacent bowel or obscuration by gallstones. However, the gallbladder wall often varies in thickness depending on where it is measured. Gallbladder wall thickening is not specific to acute cholecystitis; conversely, many patients with acute cholecystitis may not have gallbladder wall thickening (Fig 6).

Furthermore, severe gallbladder wall thickening (often circumferential with a lamellated or striated appearance reflecting edema separating wall interstices) occurs commonly with nonbiliary processes such as hypoalbuminemia, congestive heart failure, acute hepatitis, pancreatitis, or other entities that contribute to ascites (Fig 19) (50). The wall may also appear falsely thickened in the setting of underdistention (51). Thus, gallbladder wall thickening as a diagnostic criterion is limited in acute cholecystitis (10,47,51–53).

Pericholecystic Fluid

Pericholecystic fluid is often seen as a late finding of acute cholecystitis due to sympathetic fluid from gallbladder inflammation. However, pericholecystic fluid is often absent in early stages of acute cholecystitis (10). Two pitfalls of using pericholecystic fluid as a diagnostic feature are *(a)* gallbladder wall edema, which may be confused with pericholecystic fluid, and *(b)* reactive ascites from other causes such as pancreatitis, bowel inflammation, or other intra-abdominal pathologic conditions that may collect near or around the gallbladder, simulating pericholecystic fluid (7).

One location where fluid is not normal is in the bare area of the gallbladder. The bare area of the gallbladder is located between the gallbladder and liver, where there is no peritoneal covering of the gallbladder. Although rich in lymphatics, this is not a potential intraperitoneal space in which free fluid may settle. Thus, if frank fluid is seen here, gallbladder perforation may be suspected, and the gallbladder wall should be carefully scrutinized to evaluate for focal discontinuity (Fig 20).

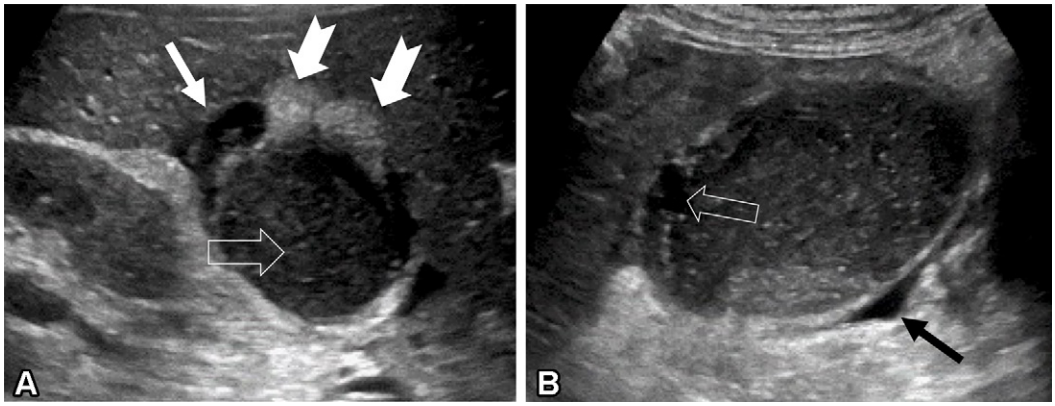

Figure 20. Perforated acute cholecystitis in a 55-year-old man. **(A)** Transverse gray-scale US image of the gallbladder shows extraluminal fluid in the bare area (thin solid arrow) and echogenic pericholecystic fat (thick solid arrows). Intraluminal sludge (open arrow) fills the entire gallbladder. **(B)** Longitudinal US image of the gallbladder shows pericholecystic fluid (black arrow) around the gallbladder separate from the fluid in the bare area. In addition, there is discontinuity (open arrow) of the normally echogenic mucosa. Care should be taken not to be deceived when the gallbladder wall is parallel to the scan line and perfectly perpendicular to the probe, as echogenic mucosa may be less evident on that view.

Putting It All Together

Acute cholecystitis can be confidently excluded if the gallbladder is nondistended (<2.2-cm width) and otherwise normal in appearance. The gallbladder is typically considered dilated if it measures greater than 4 cm in transverse dimension or greater than 8 cm in longitudinal dimension; nearly all patients with acute cholecystitis have some degree of luminal distention. Additional helpful findings in diagnosis of acute cholecystitis include the tensile fundus sign, intraluminal sludge, an impacted stone in the gallbladder neck or cystic duct, and wall hyperemia quantified with elevated cystic artery or hepatic artery velocity.

Gallbladder wall thickening and pericholecystic fluid may sometimes help but are not specific to acute cholecystitis. Findings that imply gangrenous changes or perforation include loss of mucosal sonoreflectivity, echogenic pericholecystic fat, mucosal discontinuity, and an interrupted gallbladder wall with adjacent extruded material. The sonographic Murphy sign is unreliable in clinical practice and has been historically overemphasized (Table).

Conclusion

Acute cholecystitis occurs when there is acute inflammation of an obstructed gallbladder. It is a common yet challenging diagnosis in which imaging findings in combination with physical examination findings and biochemical signs of systemic inflammation are key to making the diagnosis. No single imaging finding is definitive for acute cholecystitis in isolation. However, use of more nuanced and predictive sonographic findings of acute cholecystitis will significantly improve one's diagnostic accuracy.

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New Paradigm and Old Paradigm Imaging Findings in Diagnosis of Acute Cholecystitis

Radiologic Sign	Criteria	Pathophysiology	Details
New paradigms			
Gallbladder nondistention	Width <2.2 cm	Gallbladder can empty	Allows exclusion of acute cholecystitis
Gallbladder dilatation	Dimensions > 4 × 8 cm	Obstructed gallbladder cannot properly empty contents, leading to abnormal luminal distention (ie, dilatation)	Careful evaluation of gallbladder is warranted when dilated Gallbladder may not be dilated if perforated
Tensile fundus sign	Fundus exerts mass effect on anterior abdominal wall	Suggests high intraluminal pressure	High specificity for acute cholecystitis but less sensitive
Wall hyperemia	Cystic artery velocity (CAV) ≥ 40 cm/sec	Increased blood flow due to gallbladder wall inflammation	CAV ≥ 40 cm/sec = elevated; high PPV* for acute cholecystitis CAV 30–40 cm/sec = borderline elevated
Echogenic pericholecystic fat	Fat around gallbladder is hyperechoic compared with adjacent subcutaneous fat	Inflamed fat becomes echogenic	Indicates transmural spread of inflammation and increases likelihood of gangrenous cholecystitis
Loss of mucosal sonoreflectivity	Focal areas of decreased mucosal sonoreflectivity not attributable to technique	Ischemic mucosa is less sonoreflective	MRI and/CT equivalent: focal mucosal hypoenhancement
Wall discontinuity	Focal full thickness wall discontinuity; may see adjacent extruded fluid CEUS: interrupted wall enhancement	Perforation or impending perforation of gallbladder wall	Often associated with gallbladder decompression
Gallbladder sludge	Layering inspissated material in gallbladder lumen	Lack of periodic emptying of gallbladder leads to sludge formation	Atypical in outpatient setting and raises suspicion for gallbladder dysfunction including cholecystitis
Old paradigms			
Gallstones	Echogenic intraluminal lesions with posterior acoustic shadowing	Concentration of cholesterol exceeds solubilizing capacity of bile, leading to stone formation	Impacted gallstone in gallbladder neck or cystic duct raises suspicion for acute cholecystitis
Sonographic Murphy sign	Point of maximal tenderness corresponds to transducer located directly over gallbladder	Inflamed gallbladder is painful	Poor sensitivity (33%) and high false-negative rate due to analgesic premedication and subjectivity of assessment
Wall thickening	≥4 mm	Reactive edema of gallbladder wall	Thickness variable at different locations Not specific to acute cholecystitis Wall thickening should not be confused with pericholecystic fluid
Pericholecystic fluid	Fluid outside of but next to gallbladder wall	Inflammation leads to reactive fluid	Reactive fluid may be seen in acute cholecystitis, but other inflammatory conditions may also cause fluid Fluid in bare area beyond gallbladder wall raises concern for gallbladder perforation

* PPV = positive predictive value.

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