Wolters Kluwer

# Overview of gallstone disease in adults

**Author:** Salam F Zakko, MD, FACP, AGAF
**Section Editor:** Sanjiv Chopra, MD, MACP
**Deputy Editor:** Shilpa Grover, MD, MPH, AGAF

All topics are updated as new evidence becomes available and our peer review process is complete.

**Literature review current through:** Jun 2020. | **This topic last updated:** Apr 22, 2020.

## INTRODUCTION

Gallstones are common, particularly in Western populations [1-4]. In the United States, approximately 6 percent of men and 9 percent of women have gallstones [3]. Patients with gallstone disease may be asymptomatic or may present with biliary colic or complications of gallstone disease.

This topic will review the clinical manifestations of gallstone disease and evaluation for gallstones in a patient with biliary colic. The epidemiology of and risk factors for gallstones, the complications of gallstone disease, and the management of gallstone disease in pregnant women are discussed separately. (See "Gallstones: Epidemiology, risk factors and prevention" and "Approach to the management of gallstones" and "Gallstones in pregnancy" and "Acute calculous cholecystitis: Clinical features and diagnosis" and "Etiology of acute pancreatitis", section on 'Gallstones' and "Acute cholangitis: Clinical manifestations, diagnosis, and management" and "Choledocholithiasis: Clinical manifestations, diagnosis, and management".)

## TERMINOLOGY

**Cholecystolithiasis** — Cholecystolithiasis refers to the presence of stones in the gallbladder. The presence of stones in the gallbladder is not considered to be a disease unless they cause symptoms.

**Gallstone disease** — The term gallstone disease refers to gallstones that cause symptoms. (See 'Clinical manifestations' below.)

**Uncomplicated gallstone disease** — The term uncomplicated gallstone disease refers to biliary colic in the absence of gallstone-related complications. (See 'Biliary colic' below and 'Complications' below.)

**Complicated gallstone disease** — The term complicated gallstone disease refers to gallstone-related complications which include acute cholecystitis, cholangitis, gallstone pancreatitis, gallstone ileus, and Mirizzi syndrome. (See 'Complications' below.)

## CLINICAL MANIFESTATIONS

**Asymptomatic (incidental) gallstones** — Most individuals with gallstones are asymptomatic. In such individuals, gallstones are detected incidentally on abdominal imaging. The majority of patients found to have incidental gallstones will remain asymptomatic. Patients who develop symptoms typically report biliary colic. It is rare for a previously asymptomatic patient to present with complications of gallstone disease without first having had episodes of biliary colic. (See 'Natural history and disease course' below and 'Complications' below.)

### Symptomatic gallstones

**Biliary colic** — The classic description of biliary colic is an intense, dull discomfort located in the right upper quadrant, epigastrium, or (less often) substernal area that may radiate to the back (particularly the right shoulder blade) [5,6]. The pain is often associated with diaphoresis, nausea, and vomiting. Despite the name, the pain of biliary colic is usually constant and not colicky.

Typically, the pain has a characteristic pattern and timing for an individual patient. Eating a fatty meal is a common trigger for gallbladder contraction, and many patients report postprandial pain. However, an association with meals is not universal, and in a significant proportion of patients, the pain is nocturnal [7,8]. It is not exacerbated by movement and is not relieved by squatting, bowel movements, or passage of flatus [9]. The pain typically lasts at least 30 minutes, plateauing within an hour. The pain then starts to subside, with an entire attack usually lasting less than six hours [5]. Biliary colic is usually caused by the gallbladder contracting in response to hormonal or neural stimulation, forcing a stone (or possibly sludge) against the gallbladder outlet or cystic duct opening, leading to increased intra-gallbladder pressure. This increase in pressure then results in pain. As the gallbladder relaxes, the stones often fall back from the cystic duct, and the pain slowly subsides.

Patients with biliary colic due to uncomplicated gallstone disease are usually not ill-appearing and do not have fever or tachycardia. Laboratory test results (complete blood count,

aminotransferases, bilirubin, alkaline phosphatase, amylase, and lipase) are normal. The pain is often not severe enough to bring the patient to the emergency department. If a patient does present during a pain episode, the abdominal examination is generally benign. Biliary colic is visceral pain, and there are no peritoneal signs because the gallbladder is not inflamed. However, voluntary guarding may be encountered depending upon the severity of the pain.

The frequency of recurrent attacks is variable, ranging from hours to years, though most patients do not have symptoms on a daily basis [9]. Once a patient develops symptoms, the symptoms are likely to recur and the patient is at increased risk for the development of complications [10,11]. In an illustrative study that included 305 patients with gallstones, 70 percent of those with a history of biliary colic developed recurrent symptoms within two years [10]. (See 'Natural history and disease course' below.)

**Atypical symptoms** — Symptoms other than biliary colic have been reported in patients with gallstones, but their predictive value for the presence of gallstone disease is poor. In many cases, they may coexist with biliary colic but may or may not be related to the gallstones [12-14]. Atypical symptoms reported in patients with gallstones include:

- Belching
- Fullness after meals/early satiety
- Regurgitation
- Abdominal distension/bloating
- Epigastric or retrosternal burning
- Nausea or vomiting alone
- Chest pain
- Nonspecific abdominal pain

Patients with atypical symptoms without associated biliary colic should be evaluated for alternative diagnoses, even if gallstones are demonstrated on imaging. (See "Approach to the management of gallstones", section on 'Atypical symptoms and gallstones'.)

### Complications

**Cholecystitis** — Acute cholecystitis is the most common complication of gallstones. Acute cholecystitis refers to a syndrome of right upper quadrant pain, fever, and leukocytosis associated with gallbladder inflammation that is usually related to gallstone disease. (See "Acute calculous cholecystitis: Clinical features and diagnosis".)

Chronic cholecystitis is the term used to describe chronic inflammatory cell infiltration of the gallbladder seen on histopathology. Its presence does not correlate with symptoms since

patients with extensive chronic inflammatory cell inflammation may have only minimal symptoms, and there is no evidence that chronic cholecystitis increases the risk for future morbidity. (See "Acute calculous cholecystitis: Clinical features and diagnosis", section on 'Chronic cholecystitis'.)

**Choledocholithiasis with or without acute cholangitis** — Choledocholithiasis refers to the presence of gallstones within the common bile duct. Acute cholangitis is a clinical syndrome characterized by fever, jaundice, and abdominal pain as a consequence of infection in the setting of a biliary obstruction. (See "Choledocholithiasis: Clinical manifestations, diagnosis, and management" and "Acute cholangitis: Clinical manifestations, diagnosis, and management".)

**Gallstone pancreatitis** — The passage of gallstones through the biliary tract can trigger acute pancreatitis either by obstruction of the flow from the pancreatic duct or by obstructing the ampulla, causing bile to reflux back into the pancreatic duct. Patients present with acute pancreatitis and can have elevations in liver chemistries (bilirubin, alkaline phosphatase, and transaminases) when a gallstone transiently obstructs at the ampulla. (See "Management of acute pancreatitis", section on 'Gallstone pancreatitis' and "Etiology of acute pancreatitis", section on 'Gallstones'.)

**Other rare complications** — Other rare complications of gallstones include gallbladder cancer, gallstone ileus, and Mirizzi syndrome (impaction of a gallstone in the cystic duct, causing compression of the common bile or hepatic duct). (See "Mirizzi syndrome" and "Gallstone ileus" and "Gallbladder cancer: Epidemiology, risk factors, clinical features, and diagnosis", section on 'Gallstone disease'.)

## LABORATORY STUDIES

Laboratory studies should be normal in patients with uncomplicated gallstone disease, both during asymptomatic periods and during attacks of pain. Abnormal blood tests (leukocytosis, elevated liver tests or pancreatic enzymes) suggest the development of a complication of gallstone disease. (See 'Complications' above and "Acute calculous cholecystitis: Clinical features and diagnosis" and "Acute cholangitis: Clinical manifestations, diagnosis, and management" and "Clinical manifestations and diagnosis of acute pancreatitis".)

## EVALUATION FOR UNCOMPLICATED GALLSTONE DISEASE

**General approach** — Uncomplicated gallstone disease should be suspected in a patient with biliary colic, a normal physical examination, and normal laboratory tests (complete blood count,

aminotransferases, bilirubin, alkaline phosphatase, amylase, and lipase). Such patients should undergo an imaging study to determine if there are gallbladder stones or sludge. Typically, the evaluation begins with a transabdominal ultrasound since it is the most sensitive modality for detecting gallbladder stones.

For patients with symptoms that do not fit the classic description for biliary colic, an evaluation for non-biliary causes for the patient's symptoms should be pursued. Gallstones are sometimes implicated as the source of symptoms in patients with dyspepsia or other atypical symptoms. However, such an association should be made cautiously since gallstones may silently coexist in patients with dyspepsia and other causes of dyspepsia are more common. A general approach to the evaluation of patients with abdominal pain and dyspepsia is discussed in detail elsewhere. (See "Evaluation of the adult with abdominal pain" and "Causes of abdominal pain in adults" and "Approach to the adult with dyspepsia".)

Most patients with uncomplicated gallstone disease will have gallstones demonstrated on transabdominal ultrasound. In patients with typical biliary colic but no gallstones on ultrasonography, we usually repeat the transabdominal ultrasound in a few weeks to detect missed gallstones. The repeat examination should pay particular attention to regions of the gallbladder where stones are easily overlooked [15]. (See 'Transabdominal ultrasound' below.)

If the repeat transabdominal ultrasound is negative, we perform additional evaluation with endoscopic ultrasound, and if negative, bile microscopy to detect sludge, or microlithiasis (picture 1 and picture 2). However, the decision to pursue additional evaluation in patients with negative abdominal ultrasound imaging should be based on patient preferences, the risk for adverse outcomes with sedation and endoscopy, and the availability of endoscopic expertise. (See "Overview of upper gastrointestinal endoscopy (esophagogastroduodenoscopy)", section on 'Contraindications' and 'Endoscopic ultrasound (EUS)' below and 'Bile microscopy' below.)

Other imaging studies, including abdominal radiography and abdominal computed tomography (CT) scan, are less sensitive as compared with ultrasound for the detection of gallstones. Only 10 percent of gallstones contain enough calcium to make them sufficiently radio-opaque to be visible on a plain radiograph (image 1). Gallstones may be missed on CT because many stones are isodense with bile. The sensitivity of CT scan for gallstones ranges from 55 to 80 percent [16,17].

**Transabdominal ultrasound** — Transabdominal ultrasound is generally considered to be the most useful test to detect the presence of gallstones since it is noninvasive, readily available, relatively inexpensive, and does not subject the patient to ionizing radiation.

- **Technique** – In non-emergency settings, the examination should be conducted with the patient having fasted for at least eight hours because stones are best seen when surrounded by bile in a distended gallbladder. The entire gallbladder must be examined axially and sagittally. Every effort should be made to examine the outlet of the gallbladder (Hartmann's pouch), where gallstones may be difficult to detect. The gallbladder neck must be traced all the way into the porta hepatis to exclude stones in this region. If an out-pouching from the gallbladder (Phrygian cap) is present, the redundant portion of the fundus should be examined.

- **Imaging findings** – On ultrasound, gallstones appear as echogenic foci that cast an acoustic shadow (image 2) and seek gravitational dependency [18,19]. Gravel is the appearance of multiple small stones that are echogenic and cast shadows. Sludge is echogenic in appearance but does not cast an acoustic shadow (image 3). It is also more viscous and does not move to the dependent portion of the gallbladder as rapidly as gravel [20,21]. The sludge seen on ultrasound represents microlithiasis (lithogenic bile that contains cholesterol monohydrate crystals, bilirubin granules, and a mucus glycoprotein gel) [22,23].

  False-negative results may be obtained if the gallbladder is completely filled with stones or if it is contracted around many stones (image 4). In such cases, the findings may be confused with gas in a partially collapsed duodenal bulb, emphysematous cholecystitis, porcelain gallbladder, or a calcified hepatic artery aneurysm. Gallbladder polyps have a similar appearance to gallstones, but do not cast an acoustic shadow (image 2). (See "Gallbladder polyps and cholesterolosis".)

- **Test characteristics** – A systematic review estimated that the sensitivity was 84 percent (95% confidence interval [CI] 76 to 99 percent) and specificity was 99 percent (95% CI 97 to 100 percent) [24]. Rarely, advanced scarring and contraction of the gallbladder around gallstones leads to nonvisualization of the gallbladder lumen, which has a specificity of 96 percent, but it should also raise the possibility of gallbladder cancer.

  Modern sonographic equipment is able to detect stones as small as 1.5 to 2 mm in diameter [25]. Smaller stones may be missed, and the sensitivity falls to 50 to 60 percent for stones less than 3 mm in diameter [26-28]. This is especially true for very small stones (1 or 2 mm in diameter) that frequently, when present in large numbers, can appear on transabdominal ultrasound as one large stone. The accuracy of transabdominal ultrasonography is also operator-dependent.

  Repeating the transabdominal ultrasound increases the sensitivity for detecting stones,

particularly if they are smaller than 3 mm in diameter. (See "Clinical manifestations and diagnosis of sphincter of Oddi dysfunction" and "Approach to the adult with dyspepsia" and "Functional gallbladder disorder in adults".)

**Endoscopic ultrasound (EUS)** — EUS may identify small stones missed on abdominal ultrasound. EUS also includes an upper endoscopy, which serves to exclude other conditions (eg, peptic ulcer disease). During EUS, an ultrasound transducer on the tip of an endoscope is placed into contact with the gastric antrum, which is in close proximity to the gallbladder. This permits gallbladder visualization without interference from bowel gas, subcutaneous tissue, or the liver. As a result, EUS is more sensitive than transabdominal ultrasound for the detection of gallstones, particularly in patients who are obese or have other anatomic considerations that limit gallbladder visualization with transabdominal ultrasound [29,30]. (See 'Other tests performed in selected patients' below.)

Several studies have demonstrated that EUS is useful for the detection of small stones and microlithiasis [29-32]. In one study of 45 patients in whom there was a clinical suspicion of cholelithiasis but with at least two normal transabdominal ultrasound examinations, EUS detected cholelithiasis in 26 patients (58 percent). The sensitivity and specificity of EUS for detecting cholelithiasis were 96 and 86 percent, respectively [29]. In another study of 89 patients with acute pancreatitis, EUS revealed small gallbladder stones (1 to 9 mm) in 14 of 18 patients who had otherwise negative standard imaging studies, including transabdominal ultrasound [30]. Subsequent endoscopic retrograde cholangiopancreatography (ERCP) and cholecystectomy confirmed the presence of stones in all 14 patients.

**Bile microscopy**

- **Technique for bile collection** – Bile microscopy aims to detect microcrystals of cholesterol or amorphous bilirubinate as indirect evidence for the presence of microlithiasis in bile (picture 1 and picture 2) [33,34]. The methods for performing bile microscopy have not been standardized and few centers have the expertise to perform bile microscopy.

  Crystals are formed in the gallbladder where bile is concentrated, so gallbladder bile, rather than hepatic bile, is collected and analyzed [35-37]. We collect a bile sample during the same endoscopic session as the EUS, suctioning bile from the duodenum in the region of the ampulla after gallbladder stimulation.

  Cholecystokinin analogue, sincalide (0.03 mcg/kg body weight) is administered by intravenous infusion over 45 minutes [38]. The tip of the endoscope is positioned next to the ampulla and the bile is aspirated. Bile flow usually starts to accelerate within five

minutes of the start of the sincalide infusion. The first 5 to 10 minutes of bile flow is normally light in color and represents unconcentrated common bile duct and hepatic bile. Gallbladder bile is the darker bile that starts flowing several minutes later. We use a commercially available bile collecting catheter with a mushroom tip that is introduced through the working channel of the endoscope and connected to an external suction trap. Once dark gallbladder bile is suctioned into the collecting trap, light-colored bile is discarded from the trap and the dark bile sample is collected. Once 10 to 20 mL of bile has been collected (30 to 45 minutes), the sincalide infusion is discontinued and the procedure is concluded.

The collected sample of dark bile is incubated at 37°C for 24 hours and then centrifuged at 3000 relative centrifugal force for 30 minutes [39]. The supernatant is discarded and the sediment is mixed into the liquid remaining at the bottom of the tube. A drop of that liquid is placed on a slide and examined using a polarizing microscope; a polarizing filter facilitates identification of cholesterol crystals, which exhibit birefringence (they shine against the dark background of the polarizing microscope). The test is considered positive if any cholesterol crystals (picture 1) or amorphous (picture 2) red-brick colored bilirubinate granules are seen.

Collection during EUS is the simplest and most practical method and increases the sensitivity for detecting gallstones over that of EUS alone [29,31]. Gallbladder bile can also be collected using direct percutaneous puncture of the gallbladder under ultrasound or fluoroscopic guidance and during endoscopic retrograde cholangiopancreatography, either through selective gallbladder cannulation or by aspirating bile from the common bile duct after stimulating gallbladder contraction with a slow intravenous infusion of sincalide. (See 'Endoscopic ultrasound (EUS)' above.)

- **Test characteristics** – Bile microscopy has an overall sensitivity of 65 to 90 percent for identifying patients with gallstones [32,36,40-42]. The proportion of patients with suspected gallstones (but negative transabdominal ultrasound) found to have microlithiasis varies substantially among reports. A systematic review found that microcrystals accounted for 7 to 79 percent of cases of idiopathic pancreatitis, 83 percent of patients with unexplained biliary-type pain, and 25 to 60 percent of patients with altered biliary and pancreatic sphincter function [43].

**Other tests performed in selected patients**

- **Oral cholecystography** – Oral cholecystography can diagnose gallstones but it has largely been replaced by transabdominal ultrasound which has higher sensitivity and

specificity [24,44]. Oral cholecystography is occasionally used in patients in whom a high-quality ultrasound examination cannot be performed (eg, obese patients), and to evaluate patients who are being considered for medical dissolution therapy for gallstones. (See "Overview of nonsurgical management of gallbladder stones", section on 'Pretreatment imaging'.)

- **Cholescintigraphy (HIDA scan)** – Cholescintigraphy (99mTc-heapto-iminodiacetic acid [HIDA] scanning) is not used in the diagnosis of gallstones, but is useful in excluding acute cholecystitis in patients who present with acute biliary colic. (See "Acute calculous cholecystitis: Clinical features and diagnosis", section on 'Cholescintigraphy (hepatic iminodiacetic acid [HIDA] scan)'.)

## DIFFERENTIAL DIAGNOSIS

- **Peptic ulcer disease** – Pain in patients with peptic ulcer disease or dyspepsia is limited to the epigastrium. Patients may have associated bloating, abdominal fullness, heartburn, or nausea. (See "Peptic ulcer disease: Clinical manifestations and diagnosis", section on 'Abdominal pain'.)

- **Acute cholecystitis** – Acute cholecystitis is characterized by right upper quadrant pain, fever, and leukocytosis associated with gallbladder inflammation that is usually related to gallstone disease. The pain in patients with biliary colic is well localized and patients do not exhibit a positive Murphy's sign on physical examination. Transabdominal ultrasound findings of acute cholecystitis that are not seen in patients with uncomplicated gallstone disease include gallbladder wall thickening or edema and a "sonographic Murphy's sign". (See "Acute calculous cholecystitis: Clinical features and diagnosis", section on 'Diagnostic approach'.)

- **Choledocholithiasis** – Patients with a stone in the common bile duct (choledocholithiasis) may have typical biliary colic. However, the pain is usually more prolonged than is seen with uncomplicated gallstone disease. Serum aminotransferases are normal with uncomplicated gallstone disease but are typically elevated early in the course of biliary obstruction. If the stone is not passed, a cholestatic pattern may develop (increased bilirubin, alkaline phosphatase, and gamma-glutamyl transpeptidase out of proportion to the elevation in the aminotransferases). Patients who have developed acute cholangitis may also present with fever, leukocytosis, hypotension, or mental status changes. Transabdominal ultrasound may reveal a stone in the common bile duct or a dilated common bile duct. (See "Choledocholithiasis: Clinical manifestations, diagnosis, and

management".)

- **Sphincter of Oddi dysfunction (SOD)** – Patients with SOD may have biliary colic, but unlike patients with uncomplicated gallstone disease, patients with SOD have abnormal liver tests and/or dilation of the common bile duct. (See "Clinical manifestations and diagnosis of sphincter of Oddi dysfunction" and "Treatment of sphincter of Oddi dysfunction".)

- **Functional gallbladder disorder** – Functional gallbladder disorder is a diagnosis of exclusion. Patients with functional gallbladder disorder have biliary colic, but do not have gallstones, sludge, or microlithiasis on abdominal imaging. Functional gallbladder disorder is discussed in detail elsewhere. (See "Functional gallbladder disorder in adults".)

## NATURAL HISTORY AND DISEASE COURSE

The majority of patients with gallstones are asymptomatic and will remain so throughout their lives. Of those with incidental (asymptomatic) gallstones, approximately 15 to 25 percent will become symptomatic after 10 to 15 years of follow-up [45-49]. Patients who develop symptoms initially report biliary colic rather than symptoms associated with the complications of gallstone disease (such as cholecystitis, pancreatitis, and choledocholithiasis).

Data from large population studies indicate that once patients have biliary pain from uncomplicated disease, the risk of developing complications is approximately 2 to 3 percent per year. Once a complication develops, the risk of additional, often more severe, complications is approximately 30 percent per year [10,46-48,50,51]. (See 'Complications' above.)

Patients with asymptomatic gallstones appear to have a lower risk of complications than those with symptomatic gallstones. This was demonstrated in a study that followed 123 patients with asymptomatic gallstones and 298 patients with mild symptoms due to gallstones for up to 25 years [11]. Seven of 123 (6 percent) patients with asymptomatic stones developed severe complications. The cumulative probability of developing severe complications was lower among patients with asymptomatic gallstones compared with those with mild symptoms after 5, 10, 15, and 20 years of follow-up (4 versus 5 percent, 5 versus 12 percent, 10 versus 15 percent, and 16 versus 18 percent, respectively).

Microlithiasis (biliary sludge) can produce biliary colic and lead to complications such as acute cholangitis and acute pancreatitis [52-57]. Microlithiasis may also progress to macroscopic gallstones. (See 'Complications' above.)

## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cholecystitis and other gallbladder disorders" and "Society guideline links: Gallstones".)

## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Gallstones (The Basics)" and "Patient education: Gallbladder removal (cholecystectomy) (The Basics)")
- Beyond the Basics topics (see "Patient education: Gallstones (Beyond the Basics)")

## SUMMARY AND RECOMMENDATIONS

- The majority of patients with gallstones are asymptomatic and will remain so throughout their lives. Of those with incidental (asymptomatic) gallstones, approximately 15 to 25 percent will become symptomatic after 10 to 15 years of follow-up. (See 'Asymptomatic (incidental) gallstones' above and 'Natural history and disease course' above.)
- Patients with symptomatic uncomplicated gallstone disease typically present with biliary colic, a normal physical examination, and normal laboratory test results. Biliary colic is an intense, constant, dull discomfort usually located in the right upper quadrant or epigastrium that may radiate to the back (particularly the right shoulder blade). The pain is often associated with diaphoresis, nausea, and vomiting. (See 'Biliary colic' above.)

- Symptoms other than biliary colic have been reported in patients with gallstones, but their predictive value for the presence of gallstone disease is poor. Atypical symptoms include belching, fullness after meals/early satiety, regurgitation, abdominal distension/bloating, epigastric or retrosternal burning, nausea or vomiting, chest pain, nonspecific abdominal pain. (See 'Atypical symptoms' above.)

- Complications of gallstone disease include acute cholecystitis, choledocholithiasis with obstruction (with or without acute cholangitis), and gallstone pancreatitis. Rare complications include gallstone ileus, Mirizzi syndrome, and gallbladder cancer. (See 'Complications' above.)

- Uncomplicated gallstone disease should be suspected in a patient with biliary colic, a normal physical examination, and normal laboratory tests (complete blood count, aminotransferases, bilirubin, alkaline phosphatase, amylase, and lipase). Such patients should undergo an imaging study to determine if there are gallbladder stones or sludge. Typically, the evaluation begins with a transabdominal ultrasound since it is the most sensitive modality for detecting gallbladder stones. On ultrasound, gallstones appear as echogenic foci that cast an acoustic shadow and seek gravitational dependency. (See 'Evaluation for uncomplicated gallstone disease' above.)

- In patients with typical biliary colic but no gallstones on ultrasonography, we usually repeat the transabdominal ultrasound in a few weeks to detect missed gallstones. If the repeat transabdominal ultrasound is negative, the decision to pursue additional evaluation with endoscopic ultrasound, and if needed, bile microscopy, to detect sludge, or microlithiasis, depends on the patient's preferences, availability of endoscopic expertise, and risk factors for adverse outcomes with sedation and endoscopy. (See 'General approach' above.)

- Patients with asymptomatic gallstones appear to have a lower risk of complications than those with symptomatic gallstones. Once a complication develops, the risk of additional, often more severe, complications is approximately 30 percent per year. (See 'Natural history and disease course' above.)



## REFERENCES

1. Heaton KW, Braddon FE, Mountford RA, et al. Symptomatic and silent gall stones in the

community. Gut 1991; 32:316.

2. Zeng Q, He Y, Qiang DC, Wu LX. Prevalence and epidemiological pattern of gallstones in urban residents in China. Eur J Gastroenterol Hepatol 2012; 24:1459.

3. Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. Gastroenterology 1999; 117:632.

4. Kono S, Shinchi K, Ikeda N, et al. Prevalence of gallstone disease in relation to smoking, alcohol use, obesity, and glucose tolerance: a study of self-defense officials in Japan. Am J Epidemiol 1992; 136:787.

5. Diehl AK, Sugarek NJ, Todd KH. Clinical evaluation for gallstone disease: usefulness of symptoms and signs in diagnosis. Am J Med 1990; 89:29.

6. LUND J. Surgical indications in cholelithiasis: prophylactic choleithiasis: prophylactic cholecystectomy elucidated on the basis of long-term follow up on 526 nonoperated cases. Ann Surg 1960; 151:153.

7. Rigas B, Torosis J, McDougall CJ, et al. The circadian rhythm of biliary colic. J Clin Gastroenterol 1990; 12:409.

8. Minoli G, Imperiale G, Spinzi GC, et al. Circadian periodicity and other clinical features of biliary pain. J Clin Gastroenterol 1991; 13:546.

9. Festi D, Sottili S, Colecchia A, et al. Clinical manifestations of gallstone disease: evidence from the multicenter Italian study on cholelithiasis (MICOL). Hepatology 1999; 30:839.

10. Thistle JL, Cleary PA, Lachin JM, et al. The natural history of cholelithiasis: the National Cooperative Gallstone Study. Ann Intern Med 1984; 101:171.

11. Friedman GD, Raviola CA, Fireman B. Prognosis of gallstones with mild or no symptoms: 25 years of follow-up in a health maintenance organization. J Clin Epidemiol 1989; 42:127.

12. Zakko SF, Guttermuth MC, Jamali H, et al. A population study of gallstone composition, symptoms, and outcomes after cholecystectomy (abstract). Gastroenterology 1999; 116:A43.

13. Berger MY, Olde Hartman TC, Bohnen AM. Abdominal symptoms: do they disappear after cholecystectomy? Surg Endosc 2003; 17:1723.

14. Johnson CD. ABC of the upper gastrointestinal tract. Upper abdominal pain: Gall bladder. BMJ 2001; 323:1170.

15. Neoptolemos JP, Hall AW, Finlay DF, et al. The urgent diagnosis of gallstones in acute pancreatitis: a prospective study of three methods. Br J Surg 1984; 71:230.

16. Barakos JA, Ralls PW, Lapin SA, et al. Cholelithiasis: evaluation with CT. Radiology 1987; 162:415.

17. Benarroch-Gampel J, Boyd CA, Sheffield KM, et al. Overuse of CT in patients with complicated gallstone disease. J Am Coll Surg 2011; 213:524.

18. Leopold GR, Amberg J, Gosink BB, Mittelstaedt C. Gray scale ultrasonic cholecystography: a comparison with conventional radiographic techniques. Radiology 1976; 121:445.

19. Conrad MR, Janes JO, Dietchy J. Significance of low level echoes within the gallbladder. AJR Am J Roentgenol 1979; 132:967.

20. Brink JA, Simeone JF, Mueller PR, et al. Physical characteristics of gallstones removed at cholecystectomy: implications for extracorporeal shock-wave lithotripsy. AJR Am J Roentgenol 1988; 151:927.

21. Filly RA, Allen B, Minton MJ, et al. In vitro investigation of the origin of echoes with biliary sludge. J Clin Ultrasound 1980; 8:193.

22. Ko CW, Sekijima JH, Lee SP. Biliary sludge. Ann Intern Med 1999; 130:301.

23. Lee SP, Nicholls JF. Nature and composition of biliary sludge. Gastroenterology 1986; 90:677.

24. Shea JA, Berlin JA, Escarce JJ, et al. Revised estimates of diagnostic test sensitivity and specificity in suspected biliary tract disease. Arch Intern Med 1994; 154:2573.

25. Garra BS, Davros WJ, Lack EE, et al. Visibility of gallstone fragments at US and fluoroscopy: implications for monitoring gallstone lithotripsy. Radiology 1990; 174:343.

26. Kurol M, Forsberg L. Ultrasonography in the diagnosis of acute cholecystitis. Acta Radiol Diagn (Stockh) 1984; 25:379.

27. Venu RP, Geenen JE, Toouli J, et al. Endoscopic retrograde cholangiopancreatography. Diagnosis of cholelithiasis in patients with normal gallbladder x-ray and ultrasound

studies. JAMA 1983; 249:758.

28. Zakko SF, Srb S, Ramsby GR. Sensitivity of percutaneous endoscopy compared with ultrasonography in the detection of residue or mucosal lesions after topical gallbladder stone dissolution. Gastrointest Endosc 1995; 42:434.

29. Dahan P, Andant C, Lévy P, et al. Prospective evaluation of endoscopic ultrasonography and microscopic examination of duodenal bile in the diagnosis of cholecystolithiasis in 45 patients with normal conventional ultrasonography. Gut 1996; 38:277.

30. Liu CL, Lo CM, Chan JK, et al. EUS for detection of occult cholelithiasis in patients with idiopathic pancreatitis. Gastrointest Endosc 2000; 51:28.

31. Dill JE, Hill S, Callis J, et al. Combined endoscopic ultrasound and stimulated biliary drainage in cholecystitis and microlithiasis--diagnoses and outcomes. Endoscopy 1995; 27:424.

32. Norton SA, Alderson D. The value of endoscopic ultrasonography (EUS) in the assessme nt of idiopathic pancreatitis. In: Program and Abstracts, 11th International Symposium on Endoscopic Ultrasonography, Kyoto, Japan 1998. p.39.

33. Sedaghat A, Grundy SM. Cholesterol crystals and the formation of cholesterol gallstones. N Engl J Med 1980; 302:1274.

34. Gollish SH, Burnstein MJ, Ilson RG, et al. Nucleation of cholesterol monohydrate crystals from hepatic and gall-bladder bile of patients with cholesterol gall stones. Gut 1983; 24:836.

35. Lee SP, Nicholls JF, Park HZ. Biliary sludge as a cause of acute pancreatitis. N Engl J Med 1992; 326:589.

36. Delchier JC, Benfredj P, Preaux AM, et al. The usefulness of microscopic bile examination in patients with suspected microlithiasis: a prospective evaluation. Hepatology 1986; 6:118.

37. Corazziari E, Shaffer EA, Hogan WJ, et al. Functional disorders of the biliary tract and Pancreas. Gut 1999; 45 Suppl 2:1148.

38. Ziessman HA, Fahey FH, Hixson DJ. Calculation of a gallbladder ejection fraction: advantage of continuous sincalide infusion over the three-minute infusion method. J Nucl Med 1992; 33:537.

39. Marks JW, Bonorris G. Intermittency of cholesterol crystals in duodenal bile from gallstone patients. Gastroenterology 1984; 87:622.

40. Moskovitz M, Min TC, Gavaler JS. The microscopic examination of bile in patients with biliary pain and negative imaging tests. Am J Gastroenterol 1986; 81:329.

41. Burnstein MJ, Vassal KP, Strasberg SM. Results of combined biliary drainage and cholecystokinin cholecystography in 81 patients with normal oral cholecystograms. Ann Surg 1982; 196:627.

42. Ramond MJ, Dumont M, Belghiti J, Erlinger S. Sensitivity and specificity of microscopic examination of gallbladder bile for gallstone recognition and identification. Gastroenterology 1988; 95:1339.

43. Abeysuriya V, Deen KI, Navarathne NM. Biliary microlithiasis, sludge, crystals, microcrystallization, and usefulness of assessment of nucleation time. Hepatobiliary Pancreat Dis Int 2010; 9:248.

44. Graham EA, Cole WH, Copher GH. Visualization of the gallbladder by the sodium salt of tetrabromophthalein. JAMA 1924; 82:1777.

45. Capocaccia L, the GREPCO group. Clinical symptoms and gallstone disease: Lessons fro m a population study. In: Epidemiology and prevention of gallstone disease, Capocaccia L , Ricci G, Angelico F, Attili AF (Eds), Lancaster MTP Press, 1984. p.153.

46. Barbara L, Sama C, Morselli Labate AM, et al. A population study on the prevalence of gallstone disease: the Sirmione Study. Hepatology 1987; 7:913.

47. Gracie WA, Ransohoff DF. The natural history of silent gallstones: the innocent gallstone is not a myth. N Engl J Med 1982; 307:798.

48. Attili AF, De Santis A, Capri R, et al. The natural history of gallstones: the GREPCO experience. The GREPCO Group. Hepatology 1995; 21:655.

49. Shabanzadeh DM, Sørensen LT, Jørgensen T. A Prediction Rule for Risk Stratification of Incidentally Discovered Gallstones: Results From a Large Cohort Study. Gastroenterology 2016; 150:156.

50. Festi D, Reggiani ML, Attili AF, et al. Natural history of gallstone disease: Expectant management or active treatment? Results from a population-based cohort study. J Gastroenterol Hepatol 2010; 25:719.

51. Ransohoff DF, Gracie WA. Treatment of gallstones. Ann Intern Med 1993; 119:606.

52. Venu RP, Geenen JE, Hogan W, et al. Idiopathic recurrent pancreatitis. An approach to diagnosis and treatment. Dig Dis Sci 1989; 34:56.

53. Lee SP, Maher K, Nicholls JF. Origin and fate of biliary sludge. Gastroenterology 1988; 94:170.

54. Neoptolemos JP, Davidson BR, Winder AF, Vallance D. Role of duodenal bile crystal analysis in the investigation of 'idiopathic' pancreatitis. Br J Surg 1988; 75:450.

55. Geenen JE, Nash JA. The role of sphincter of Oddi manometry and biliary microscopy in evaluating idiopathic recurrent pancreatitis. Endoscopy 1998; 30:A237.

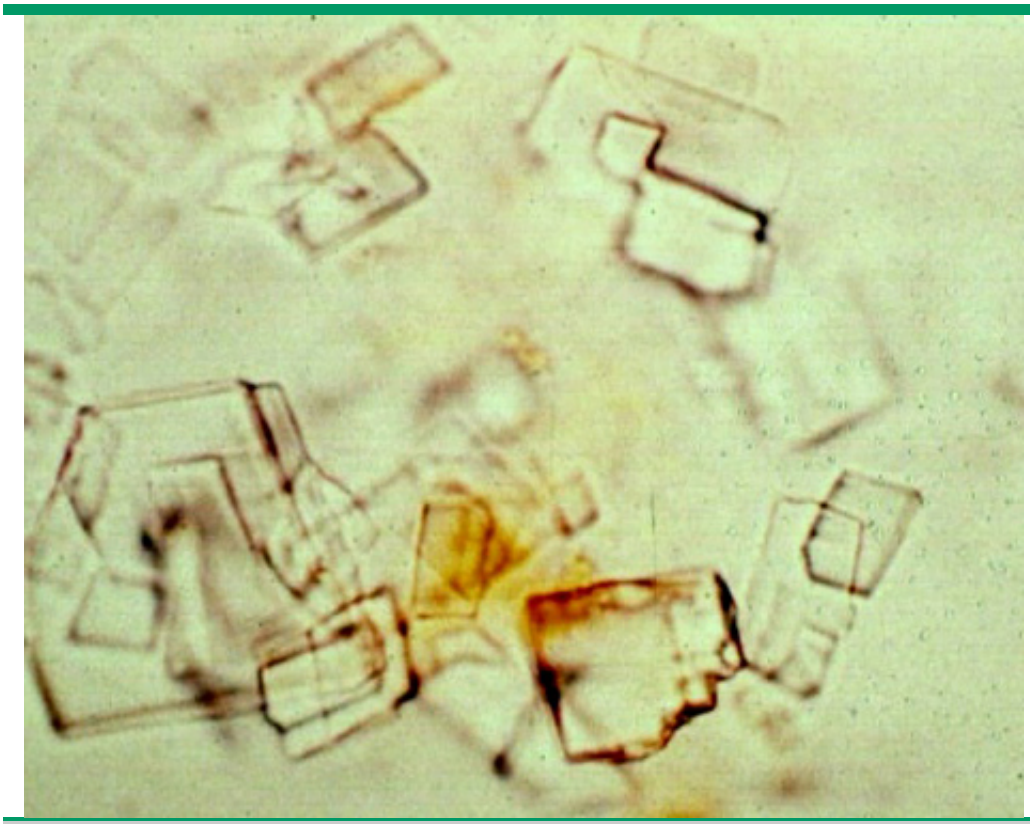
56. Basaranoglu M, Balci NC. Recurrent cholangitis associated with biliary sludge and Phrygian cap anomaly diagnosed by magnetic resonance imaging and magnetic resonance cholangiopancreatography despite normal ultrasound and computed tomography. Scand J Gastroenterol 2005; 40:736.

57. Corazziari E, Shaffer EA, Hogan WJ, et al. Functional disorders of the biliary tract and pancreas. Gut 1999; 45 Suppl 2:II48.

Topic 654 Version 41.0

## GRAPHICS

### Gallbladder bile microscopy

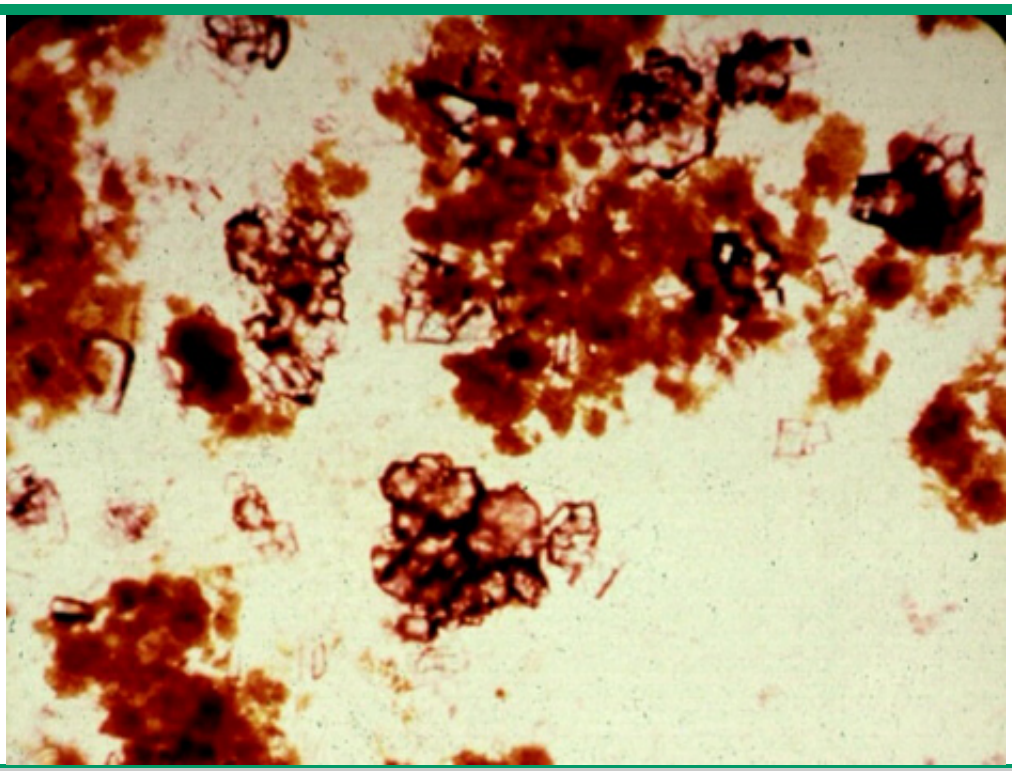


Cholesterol crystals on microscopy. Note the rhomboid appearance with the notch on one corner.

*Courtesy of Salam F Zakko, MD, FACP.*

Graphic 73479 Version 2.0

## Gallbladder bile microscopy

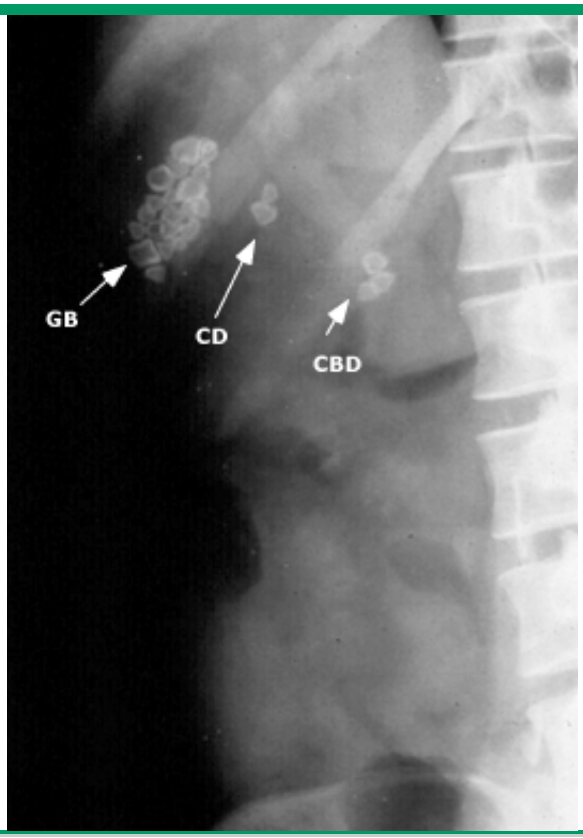


Amorphous brown bilirubinate crystals on microscopy.

*Courtesy of Salam F Zakko, MD, FACP.*

Graphic 80050 Version 2.0

## Calcified gallstones

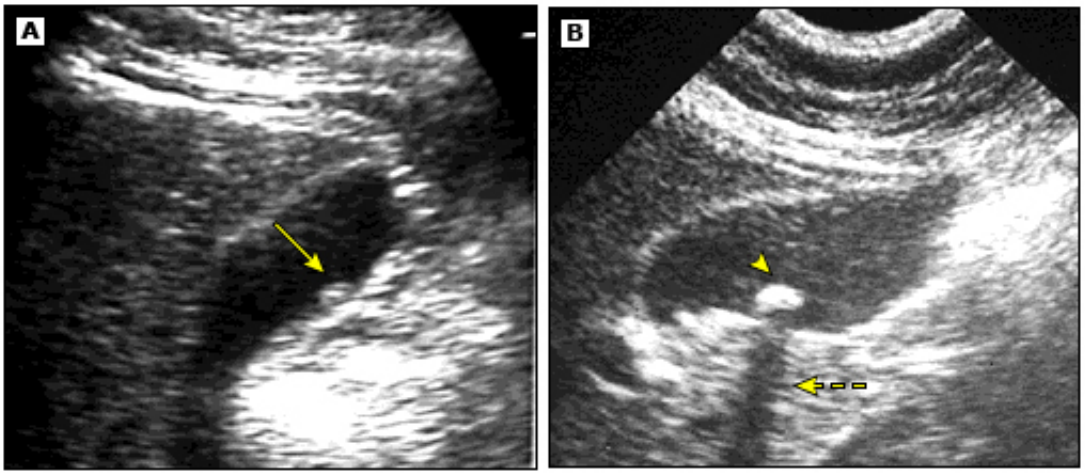



A plain abdominal x-ray showing calcified gallstones in the gallbladder (GB), cystic duct (CD) and common bile duct (CBD).

*Courtesy of Salam F Zakko, MD, FACP, AGAF.*

Graphic 71203 Version 3.0

## Gallbladder polyp versus gallstone on ultrasound

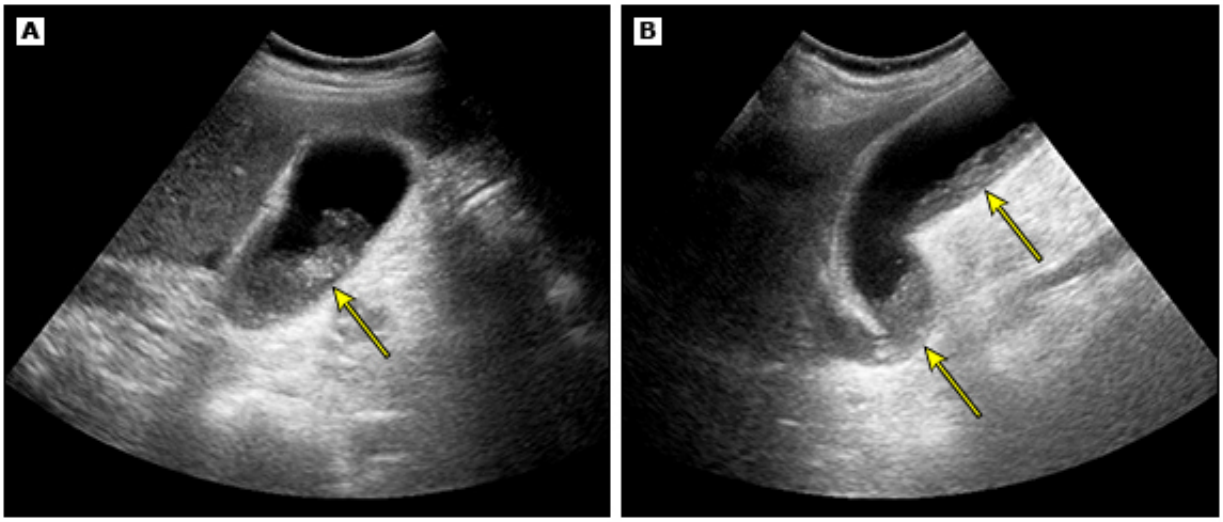



Ultrasound images of a gallbladder adenomatous polyp (arrow) compared with a gallstone (arrowhead). Note the shadow cast by the stone (dashed arrow) compared with the absence of a shadow behind the polyp.

*Courtesy of Salam F Zakko, MD, FACP.*

Graphic 70175 Version 4.0

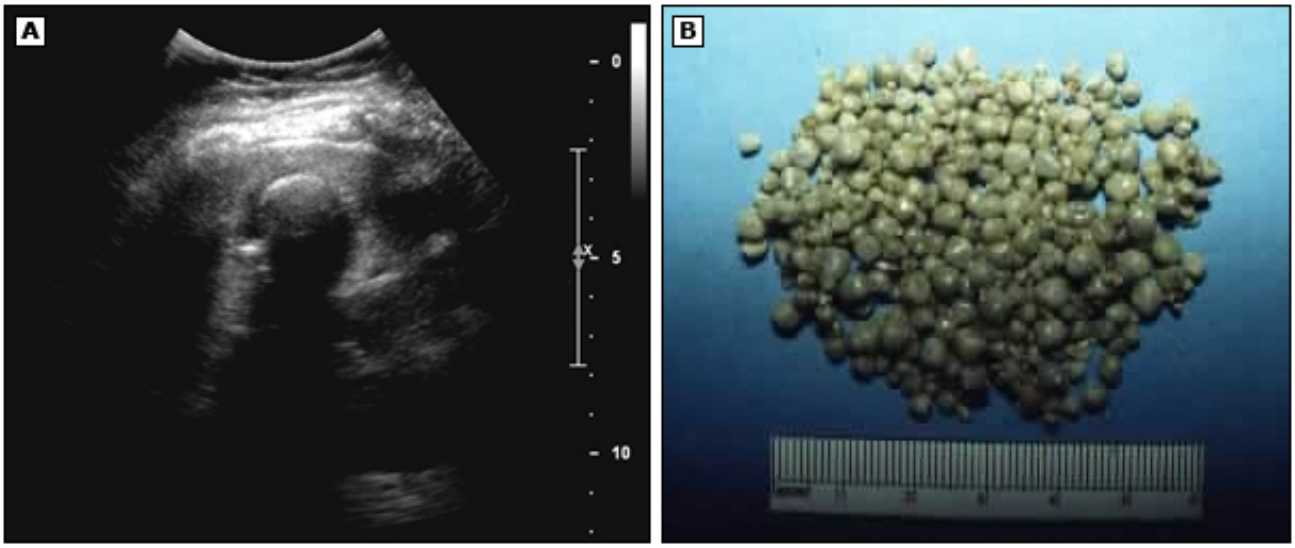
## Gallbladder sludge on ultrasonography




Ultrasonography images in a patient with gallbladder sludge.
(Panel A) A large amorphous collection of sludge within the gallbladder (arrow) that does not cast an acoustic shadow.
(Panel B) When the patient was turned onto one side, the gallbladder sludge formed a layer along the dependent portion of the gallbladder (arrows).

Graphic 88946 Version 1.0

## Misleading ultrasound in a patient with gallstones




(A) This ultrasound was obtained from a patient with a gallbladder that contained numerous gallstones. On ultrasound, the stones appear as one large concretion or gas.
(B) Multiple stones were found in the gallbladder after cholecystectomy.

*Courtesy of Salam F Zakko, MD, FACP, AGAF.*

Graphic 97751 Version 2.0

## Contributor Disclosures

**Salam F Zakko, MD, FACP, AGAF** Nothing to disclose **Sanjiv Chopra, MD, MACP** Nothing to disclose **Shilpa Grover, MD, MPH, AGAF** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy