Overview of nonsurgical management of gallbladder stones

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INTRODUCTION

The majority of patients with asymptomatic (incidental) gallstones do not require treatment. Patients with symptomatic gallstone disease who are unable or unwilling to undergo cholecystectomy may be candidates for nonsurgical management. (See "Overview of gallstone disease in adults", section on 'Symptomatic gallstones'.)

For patients with symptomatic gallstones who are surgical candidates, cholecystectomy is the treatment of choice in order to prevent future attacks of biliary colic and complications of gallstone disease [1-3]. While the nonsurgical approaches are hypothetically safer, requiring no abdominal incision or general anesthesia, they all suffer from three inherent disadvantages. They are labor-intensive, they are mainly suited for primarily cholesterol stones, and they have high rates of recurrence.

The main modalities for nonsurgical treatment of gallbladder stones include oral dissolution therapy with bile acids, and percutaneous cholecystostomy and stone extraction. Extracorporeal shock wave lithotripsy (ESWL) is used in rare situations. Historically, topical solvent dissolution was widely used but it is labor-intensive, expensive, and requires a complex apparatus for safe solvent delivery that is not readily available [4-7]. This topic will review nonsurgical management for gallbladder stones. Nonsurgical management of bile duct stones (choledocholithiasis) and cholangitis, including endoscopic sphincterotomy without subsequent cholecystectomy, are

discussed separately. (See "Endoscopic management of bile duct stones" and "Laparoscopic cholecystectomy".)

TYPES OF GALLSTONES

Composition — Gallstones are composed of a mixture of cholesterol, calcium salts of bilirubinate or palmitate, proteins, and mucin. Based upon the predominant constituents, gallstones are broadly classified into the following (picture 1):

- **Cholesterol stones** – Cholesterol stones usually form in individuals with a genetic or environmental predisposition to bile that is supersaturated with cholesterol. Most "cholesterol" stones have a mixed composition with small amounts of calcium, palmitate, and bilirubinate salts.
- **Black pigment stones** – Black pigment stones result from hemolysis and consist primarily of calcium bilirubinate.
- **Brown pigment stones** – Brown pigment stones are associated with a bacterial infection or parasitic infestation of the biliary system. They are also often found in the bile ducts in association with prior biliary manipulation. They may also occur as de novo common bile duct stones following cholecystectomy.

Gallstones in an individual patient are usually similar in composition.

Prevalence by composition — The prevalence of pigment stones is dependent primarily upon the frequency of hemolytic disorders in the community. In industrialized countries, cholesterol gallstones account for approximately 75 percent of stones, black pigment stones for 20 percent, and brown pigment stones for 5 percent [8-12].

PRETREATMENT IMAGING

Pretreatment imaging of the gallbladder is required to guide the choice of nonsurgical management options. Imaging is needed to evaluate:

- Composition of the gallstones
- Number and size of stones within the gallbladder
- Patency of the cystic duct
- The concentrating ability of the gallbladder

We use a noncontrast thin slice computed tomography (CT) limited to the gallbladder to evaluate gallstone composition. We use an oral cholecystogram or HIDA scan to assess cystic duct patency. An oral cholecystogram can also assess gallbladder wall concentrating ability. We do not assess gallbladder motor function with cholecystokinin-stimulated imaging (HIDA scan/oral cholecystogram/ultrasound) in patients with known gallstones as this can lead to biliary colic.

Transabdominal ultrasonography is often the first test for the diagnosis of gallstones. It should be interpreted with caution as it may not accurately determine the number or size of stones in the gallbladder. Smaller stones might be missed (1 or 2 mm in diameter) and, when present in large numbers, can appear on transabdominal ultrasound as one large stone, which would erroneously lead to the conclusion that the patient is not an ideal candidate for dissolution therapy. Hence, we use it in combination with the CT scan findings for this purpose. When available, the oral cholecystogram is the most accurate test for evaluating stone size and number. (See "Overview of gallstone disease in adults", section on 'Transabdominal ultrasound'.)

Computed tomography — A limited noncontrast CT scan without oral or intravenous contrast and of only the liver and gallbladder can assess stone composition by evaluating buoyancy (relative physical density of the stones to bile) and CT image density in Hounsfield units (image 1) [13-16]. The presence of floating stones (gallstone buoyancy) is indicative of high cholesterol gallstone content and relatively more rapid dissolution. Stones with a high concentration of cholesterol have a very low CT density and appear as black holes within gallbladder bile (image 1). Stones with an average CT density of <75 Hounsfield units are the most susceptible to dissolution, whereas stones with an average CT density of >100 Hounsfield units dissolve poorly [13].

The pattern of calcification and the stone's morphologic appearance on CT scan may also be predictive of dissolution success [14]. Highly calcified stones and stones with dense surface calcification are unlikely to dissolve. The majority of gallstones are not visualized on abdominal CT because they are isodense with bile. However, assessing the CT density of bile in the gallbladder in this case can help predict outcomes. (See 'Efficacy' below.)

Oral cholecystography — Oral cholecystography can accurately assess the number of gallstones, their size, buoyancy, cystic duct patency, and the gallbladder's concentrating ability (image 2) [17,18]. Cholecystography involves administration of an oral contrast agent (eg, iopanoic acid, sodium tyropanoate, or calcium ipodate) the night before the test. It is absorbed through the intestine, taken up by the liver, secreted into bile, and concentrated in the gallbladder. Successful visualization of the gallbladder on abdominal upright radiographs the

next day is based on all these steps being intact. Oral cholecystography can also indirectly assess gallbladder motor function. A reduction in gallbladder size on serial radiographs after ingestion of a fatty meal suggests that the gallbladder is functioning normally.

On plain radiographs, gallstones appear as filling defects within the contrast. Gallstone buoyancy, which is indicative of high cholesterol contention, can be seen in the upright position (image 2). Non-opacification of the gallbladder can occur due to poor absorption from the intestine, liver disease with impaired hepatic clearance of iminodiacetic acid compounds, impaired gallbladder concentration due to mucosal fibrosis, or extrahepatic biliary obstruction. The availability of the contrast agents for this test has been sporadic. When not available, we rely on the other imaging studies from which we can derive adequate, although slightly less accurate, information.

Cholescintigraphy (HIDA scan) — We perform cholescintigraphy using 99mTc-hepatic iminodiacetic acid (generically referred to as a HIDA scan) to assess cystic duct patency only if an oral cholecystogram is not available. Unlike oral cholecystography, the HIDA scan cannot assess mucosal concentration function of the gallbladder, as the tracer will enter the gallbladder, leading to its visualization without the need for concentration. A stimulated HIDA scan with cholecystokinin should not be performed in patients with known gallbladder stones, as a forceful gallbladder contraction may lead to an attack of biliary colic or other complications. (See "Acute calculous cholecystitis: Clinical features and diagnosis", section on 'Cholescintigraphy (hepatic iminodiacetic acid [HIDA] scan)'.)

MANAGEMENT

Choice of therapy — The goal of nonsurgical management is to reduce the severity of symptoms, clear the gallbladder of stones, and/or decrease the risk of gallstone-related complications. The choice of non-surgical options is based on the clinical presentation and stone/gallbladder characteristics as assessed by imaging and patient preferences. (See 'Pretreatment imaging' above and "Overview of gallstone disease in adults", section on 'Symptomatic gallstones'.)

In symptomatic patients with uncomplicated gallstone disease, manifested by biliary colic, who are unable/unwilling to undergo cholecystectomy and have small noncalcified stone(s) in a functioning gallbladder, we suggest oral bile acid dissolution therapy with ursodeoxycholic acid. Ideal candidates for oral bile acid dissolution therapy have all the following characteristics [19-24]:

- Small stone size (<1 cm)
- Minimal stone calcification and high cholesterol concentration
- Mild symptoms of uncomplicated gallstone disease (biliary colic)
- Patent cystic duct
- Good gallbladder mucosal concentration function

In symptomatic patients with uncomplicated gallstone disease who are unable/unwilling to undergo cholecystectomy but who do not have small noncalcified stones, the decision to use oral dissolution therapy is made on an individual basis, taking into account patient preferences and success rates for dissolution therapy. As an example, patients with larger stones may be treated with oral dissolution therapy but will require several years of therapy for dissolution. (See 'Efficacy' below.)

In patients with unremitting biliary colic that is unresponsive to oral bile acid therapy, percutaneous extraction via a cholecystostomy tube can be performed if they are unable/unwilling to undergo cholecystectomy. In patients with acute cholecystitis who require percutaneous gallbladder drainage, percutaneous gallstone extraction can be performed in patients who continue to be high risk for surgery. (See "Treatment of acute calculous cholecystitis", section on 'Percutaneous' and "Approach to the management of gallstones", section on 'Alternatives to cholecystectomy'.)

Oral bile acid dissolution therapy

Mechanism of action — Ursodeoxycholic acid (ursodiol) dissolves gallstones by solubilizing cholesterol from the surface and center of the gallstone. In addition, ursodiol has been shown to inhibit and reduce intestinal absorption of cholesterol and improve gallbladder emptying [20,25-29]. When the cholesterol portion of stones that have limited amounts of calcium salts dissolve, the remainder of the stone disintegrates into sand that is expelled over time by a functioning gallbladder.

For ursodiol to be effective, a patent cystic duct is required for it to enter the gallbladder. The absorptive capacity of the gallbladder is important to the successful stone dissolution, as bile acid entering the gallbladder needs to be concentrated in order for it to dissolve the cholesterol. Good gallbladder motor function (ie, filling and emptying) is theoretically desirable to ensure that bile that has become saturated with the dissolved cholesterol is emptied into the duodenum and fresh, unsaturated hepatic bile containing the administered bile acid can mix with the stones and affect their dissolution. Good motor function is also needed to expel gallstone debris and minimize stone recurrence. (See 'Gallstone recurrence' below.)

Dose and administration — Ursodiol is typically given at a dose of 10 mg/kg daily in two to three divided doses [30-32]. Administration in divided doses helps maintain hepatic bile acid secretion overnight, reduces secretion of supersaturated bile, and increases stone dissolution rates [33,34].

Monitoring and duration — We perform an abdominal ultrasound every 6 to 12 months to assess the response to oral dissolution treatment. However, it is important to note that because most stones dissolve from the inside out, they do not appear to be decreasing in size on yearly follow-up exams before they disappear when the external shell disintegrates. Ursodiol is continued for at least six months after ultrasonography demonstrates clearance of the gallstones. In patients in whom high surgical/anesthetic risk precludes cholecystectomy, we continue long-term therapy. (See 'Prevention of recurrence' below.)

The rate of gallstone dissolution in patients taking ursodiol at a standard dose is approximately 1 mm per month [35]. Multiple small stones dissolve faster than a few larger stones due to their larger surface area. If only patients with ideal characteristics were selected (small, noncalcified, high cholesterol stones in a functioning gallbladder), dissolution rates may exceed 90 percent [36]. Unfortunately, less than 10 percent of patients fall into this category. The response to treatment is slow and treatment may be required for two or more years. However, in most cases, recurrent uncomplicated biliary colic will subside within a few weeks of bile acid administration even though the stones are still present [23,24].

Efficacy — The results of oral dissolution therapy correlate with the size and composition of the gallstones. The overall success rate for ursodiol in dissolving gallstones up to 20 mm in diameter ranges from 30 to 50 percent [20]. A meta-analysis of 23 randomized trials found a 37 percent dissolution rate with ursodiol, with higher dissolution rates in patients with small buoyant stones [37]. Incomplete dissolution has been attributed to insoluble components of the gallstones as well as a process referred to as "rim calcification," in which calcium is laid down upon the surface of the stone, preventing the bile acid from reaching the cholesterol portion of the stones. Rim calcification has been reported in 10 to 12 percent of patients treated with bile acids [38,39].

In most cases, episodes of biliary pain decrease in frequency within a few weeks of bile acid administration even though gallstones are still present [21,23,24,30,40-42]. This observation was supported by a cohort study that included 527 patients with uncomplicated gallstones of whom 181 received ursodiol who were followed for up to 18 years [21]. The use of ursodiol was associated with a significantly reduced risk of gallstone-related symptoms at up to 10 years of follow-up (62 versus 92 percent in those with a history of gallstone-related symptoms, and 6 versus 12 percent in those without a prior history of symptoms). This benefit was independent

of stone dissolution. Although this study is limited by its nonrandomized design, it suggests a potential benefit of long-term bile acid therapy in symptomatic patients even if complete gallstone dissolution cannot be accomplished. (See 'Monitoring and duration' above.)

Percutaneous cholecystostomy and gallstone extraction — In patients with a percutaneous cholecystostomy tube for gallbladder drainage but who remain at high risk for surgery, gallstones can be extracted percutaneously. This is typically performed two or more weeks after placement of the cholecystostomy thereby, allowing time for the development of an epithelialized percutaneous tract that extends into the gallbladder [43]. The tract is dilated under fluoroscopic guidance using graded percutaneous dilators followed by basket extraction of the stones and irrigation of the debris to the outside using saline [44]. Percutaneous cholecystoscopy has been used to monitor and aid this procedure [45-47]. (See "Treatment of acute calculous cholecystitis", section on 'Nonsurgical candidates'.)

THERAPIES WITH LIMITED OR UNCERTAIN BENEFIT

Extracorporeal shock wave lithotripsy (ESWL) — Solitary, radiolucent stones are technically amenable to fragmentation with ESWL. However, the use of ESWL is limited by high rates of biliary colic (30 to 50 percent) and high rates of gallstone recurrence (up to 60 percent at 5 years) after treatment [48-50]. ESWL employs shock waves produced by electrical discharge. These shock waves generated outside the body are focused on the gallstones, using acoustic reflectors, to fragment the stone. Stone fragments are then ejected into the duodenum through the biliary system [16,51]. The success rates of ESWL decrease in the presence of multiple stones, impaired gallbladder motor function, and the presence of gallstone calcifications [52]. The use of oral bile acids as an adjunctive measure to ESWL does not appear to be superior to ESWL alone in providing symptom relief [53]. (See 'Oral bile acid dissolution therapy' above.)

Statins — There is insufficient evidence to recommend the use of statins for the treatment of gallstones. Statins reduce biliary cholesterol secretion and long-term use of statins is associated with a reduction in gallbladder disease [54-61]. However, the efficacy of statins in gallstone dissolution has not been demonstrated [62]. Results from randomized trials combining statins with ursodiol have also been conflicting [63,64].

Ezetimibe — Ezetimibe is a lipid-lowering drug that acts by inhibiting intestinal cholesterol absorption. Animal models suggest that it may be effective for the treatment or prevention of gallstones [65,66]. It lowers biliary cholesterol secretion but does not decrease the bile salt content in bile. In humans it has been shown to reduce the cholesterol saturation index of bile

and slow cholesterol crystallization [65]. Clinical trials are needed to determine if it is effective for gallstone prevention or dissolution.

Monoterpenes — Monoterpenes stimulate bile production and increase the solubility of cholesterol, calcium carbonate, and calcium phosphate. A preparation of six monoterpenes has been used in combination with chenodeoxycholic acid dissolution therapy for radiolucent and some radio-opaque gallstones [67,68]. While it appears to be well tolerated, its efficacy has not been evaluated in randomized trials.

GALLSTONE RECURRENCE

Incidence — Gallstone recurrence following successful medical therapy remains a major concern because patients frequently remain poor surgical candidates. Gallstone recurrence rates at five years in patients treated with oral dissolution or extracorporeal shockwave lithotripsy are 45 and 60 percent, respectively [48,49,69-73]. However, recurrent stones are usually asymptomatic and appear to follow the natural history of asymptomatic stones. In patients treated with oral bile acid dissolution therapy, the risk of recurrence appears to be highest in those with multiple stones and in whom the time to complete dissolution was longest [69].

Recurrent gallstones are often cholesterol rich and not necessarily the same composition as the initial gallstones. Even in the case of previous calcified gallstones, recurrent gallstones are usually rich in cholesterol, and may be suitable for oral bile acid dissolution therapy [74]. However, recurrent stones are usually asymptomatic and may not need therapy unless they cause symptoms. (See "Overview of gallstone disease in adults", section on 'Natural history and disease course'.)

Prevention of recurrence — In addition to dietary and lifestyle modification, we continue long-term oral bile acid dissolution therapy in patients who are unable or unwilling to undergo cholecystectomy and are at risk for recurrent gallstones. Long-term bile acid therapy is likely to prevent further gallstone recurrence and the development of symptoms [20,75,76]. (See "Gallstones: Epidemiology, risk factors and prevention", section on 'Risk factors'.)

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: 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: Choosing surgery to treat gallstones (The Basics)")
- Beyond the Basics topics (see "Patient education: Gallstones (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- The majority of patients with asymptomatic (incidental) gallstones do not require treatment. Patients with symptomatic gallstone disease or those at high risk for developing symptomatic gallstone disease, but are unable or unwilling to undergo cholecystectomy, may be candidates for nonsurgical management. (See 'Introduction' above.)
- Gallstones are composed of a mixture of cholesterol, calcium salts of bilirubinate or palmitate, proteins, and mucin. Based upon the predominant constituents, gallstones are broadly categorized into cholesterol, brown pigment, and black pigment stones. (See 'Composition' above.)
- Dedicated imaging of the gallbladder is required to evaluate the number and size of stones within the gallbladder and their composition, the patency of the cystic duct, and the concentrating ability of the gallbladder. This can usually be achieved by a combination of computed tomography and oral cholecystography/cholescintigraphy of the gallbladder. (See 'Pretreatment imaging' above.)

- The goal of nonsurgical management is to reduce the severity of symptoms, clear the gallbladder of stones, and decrease the risk of gallstone related complications. The choice of nonsurgical therapy is based the clinical presentation and stone/gallbladder characteristics as assessed by imaging and patient preferences. (See 'Choice of therapy' above.)

- Ideal candidates for oral bile acid dissolution therapy have all the following characteristics:

  - Small stone size (<1 cm)
  - Minimal stone calcification and high cholesterol concentration
  - Mild symptoms of uncomplicated gallstone disease (biliary colic)
  - Patent cystic duct
  - Good gallbladder mucosal concentration function

- We suggest oral bile acid dissolution therapy with ursodeoxycholic acid (ursodiol) in patients with mild symptoms who have non-calcified small stone(s) in a functioning gallbladder and are not candidates for cholecystectomy (**Grade 2B**). The decision to use oral bile acid dissolution therapy in symptomatic patients with uncomplicated gallstone disease who are unable/unwilling to undergo cholecystectomy but do not have small noncalcified stones is made on an individual basis taking into account patient preferences. (See 'Choice of therapy' above.)

- We perform an abdominal ultrasound every 6 to 12 months to assess the response to oral dissolution treatment. Ursodiol is continued for at least six months after sonographic clearance of the gallstones. In patients at high surgical/anesthetic risk for cholecystectomy, we continue long-term therapy. (See 'Monitoring and duration' above and 'Prevention of recurrence' above.)

- We reserve percutaneous stone extraction in patients with a cholecystostomy tube either for recurrent symptoms of biliary colic despite oral dissolution treatment or complicated gallstone disease (acute cholecystitis) who cannot undergo surgery. Solitary, radiolucent stones are technically amenable to fragmentation with extracorporeal shock wave lithotripsy (ESWL). However, the use of ESWL is limited by high rates of biliary colic and gallstone recurrence after treatment. (See 'Percutaneous cholecystostomy and gallstone extraction' above and 'Extracorporeal shock wave lithotripsy (ESWL)' above.)

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GRAPHICS

Gallstones

Gallstones retrieved from six different patients. Note how gallstones are similar in the same patient but differ among patients.

(A-D) Cholesterol stones.

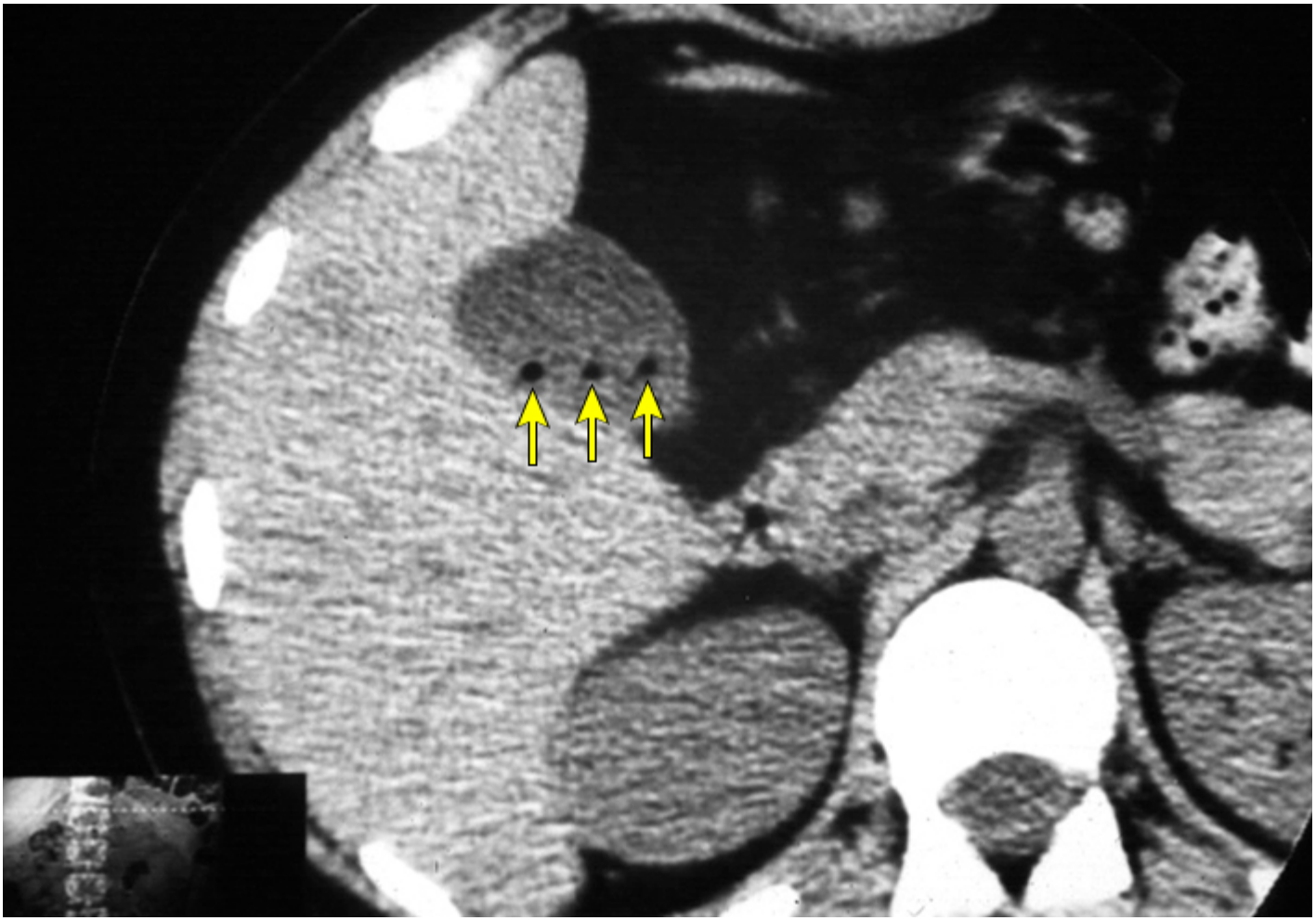
(E) Brown pigment stones.

(F) Black pigment stones.

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

Graphic 114842 Version 3.0

Abdominal computed tomography scan of gallstones

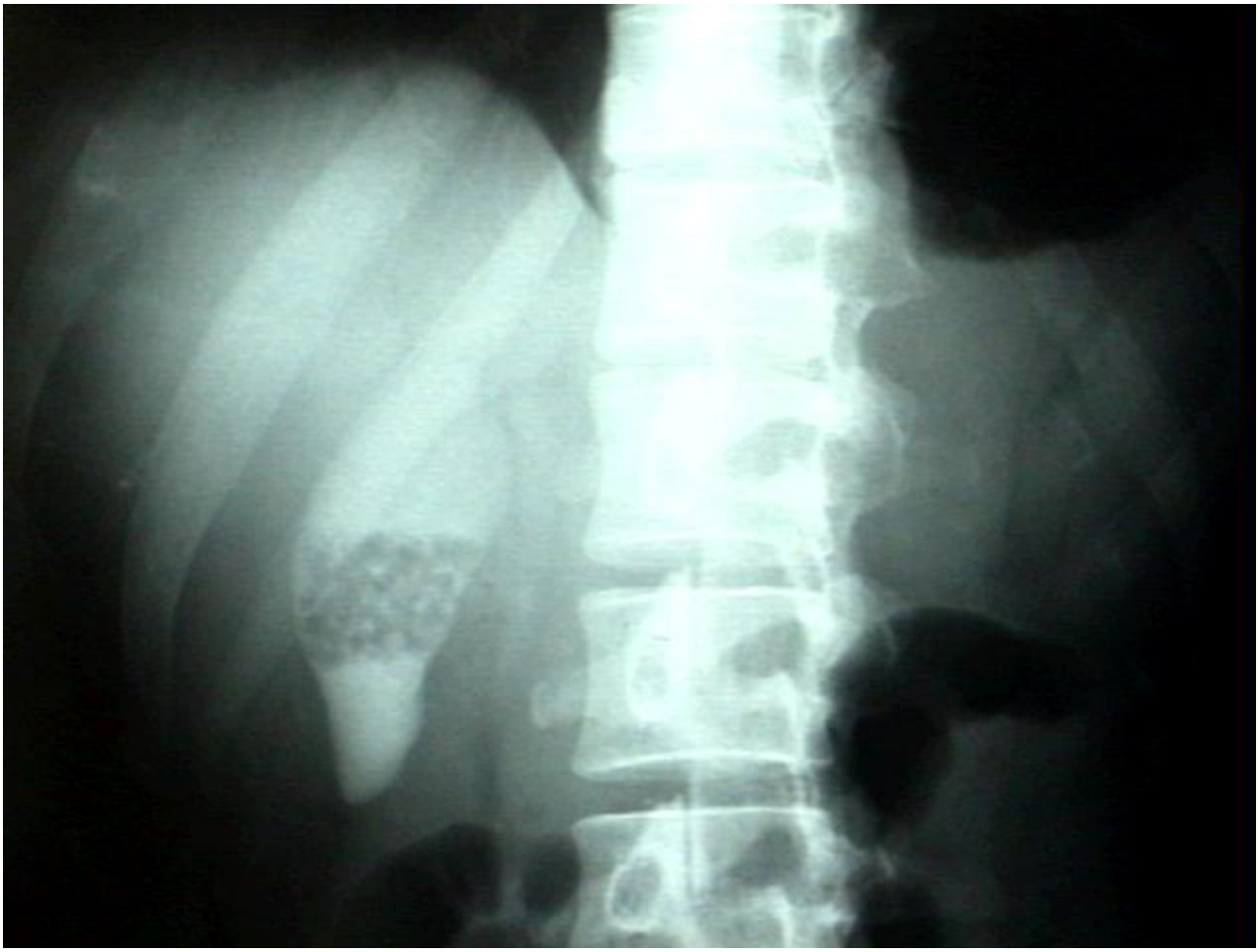


An abdominal computed tomography scan image with floating cholesterol stones layering in the center of t gallbladder. Note how pure cholesterol stones appear like black holes (arrows) within gallbladder bile due tc very low computed tomography density of cholesterol.

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

Graphic 114841 Version 3.0

Oral cholecystogram with gallstones



An oral cholecystogram in the upright position showing a gallbladder that is outlined by contrast with layers of floating gallstones in its center.

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

Graphic 114838 Version 2.0

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