

Gallstones

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Educational Goals

By the end of this lecture you should be familiar with:

1. Pathogenesis and types of gallstones.
2. Clinical manifestations of gallstones.
3. Approach to the diagnosis of gallstones and their related morbidity.
4. Treatment modalities for gallstone disease.

Key Words

- acute cholecystitis
- acute pancreatitis
- ascending cholangitis
- asymptomatic gallstones
- bile acids
- biliary colic
- black pigment stones
- Boas' sign
- brown pigment stones
- cholecystectomy
- choledocholithiasis
- cholesterol
- cholesterol stones
- cholesterol-7-hydroxylase
- cholestyramine
- chronic hemolytic condition
- endoscopic ultrasound
- ERCP
- estrogen-replacement therapy
- gallbladder hypomotility
- gallbladder sludge
- hepatobiliary scan (HIDA)
- HMG-coA reductase
- ileal disease
- laparoscopic cholecystectomy
- lecithin
- microlith
- MRI/MRCP
- mucin glycoprotein
- Murphy's sign
- nucleation
- octreotide
- oral contraceptives
- porcelain gallbladder
- primary bile duct stones
- radiolucent
- radiopaque
- secondary bile duct stones
- sickle cell anemia
- somatostatin
- sphincterotomy
- supersaturation
- thalassemias
- TPN
- ultrasonography
- unconjugated bilirubin
- ursodeoxycholic acid

General Overview

In the United States over 10% of the total population has gallstones. Each year 1,000,000 new patients are diagnosed. Performance of 500,000 cholecystectomies leads to an annual expense of more than \$5 billion in direct costs.

Epidemiology

- A. Gallstone prevalence varies with age and gender, ethnic group and family history.
- B. *Gender*: The female: male ratio is 2:1 in the younger population. Childbearing, estrogen-replacement therapy, and oral contraceptives increase the risk of developing gallstones.
- C. *Age*: Gallstone prevalence increases in both sexes with age. After the age of 60, 10-15% men and 20-40% women have gallstones.
- D. *Ethnicity*: Gallstone prevalence is especially high in certain populations and regions of the world. Some of the highest incidence of gallstone disease is seen in the Scandinavian countries, Chile and among Native Americans. Populations at low risk are sub-Saharan Africa and Asia. African-Americans have a lower prevalence than whites.
- E. *Family History*: Within a given population first degree relatives of persons with gallstones have a 4.5 times greater likelihood to develop gallstones than are matched controls,

- F. *Additional factors:* The incidence is higher in markedly obese individuals and in those who lose weight rapidly. Gallstones are more frequent among patients with certain diseases such as: regional enteritis (Crohn's disease), cirrhosis of the liver and chronic hemolytic conditions.

Pathogenesis of Gallstones

There are three types of gallstones each with varying amounts of cholesterol, bilirubin, calcium salts, protein and other materials: **Black pigment Stones, Brown pigment stones and Cholesterol stones.**

1. **Black pigment stones** (bilirubin stones)
 - a. Consist of polymers of calcium bilirubinate, with large amounts of mucoprotein.
 - b. Usually contain less than 10% cholesterol.
 - c. Contain 30-60% unconjugated bilirubin by weight. Unconjugated bilirubin is not water soluble, while conjugated bilirubin is water-soluble.
 - d. 50% are radiopaque, 50% are radiolucent (stones that are more than 4% calcium by weight are radiopaque).
 - e. Are common in patients with cirrhosis and chronic hemolytic conditions, such as the thalassemias and possibly sickle cell anemia, in which bilirubin excretion is increased.
2. **Brown pigment stones**
 - a. Are made of Ca salts of unconjugated bilirubin, with variable amounts of protein and cholesterol.
 - b. Are usually primary bile duct stones
 - c. Are usually associated with biliary infection. Bacteria in the biliary system release glucuronidases, which hydrolyze glucuronic acid from conjugated bilirubin. The resulting unconjugated bilirubin precipitating as its calcium salt.
 - d. Are more prevalent in Asians, associated with decreased secretory IgA.
3. **Cholesterol stones**
 - a. 75-80% of gallstones in this country are classified as cholesterol (non-pigmented) stones. Almost all cholesterol stones are radiolucent. Cholesterol is the major component (usually greater than 70% by weight).
 - b. Cholesterol-saturated bile is a prerequisite for the formation of cholesterol gallstones, and the incidence of gallstones within a population is correlated with the prevalence of saturated bile.
 - c. The solubility of cholesterol is determined primarily by the relative proportions of bile acids, lecithin, and cholesterol in the bile. Thus, anything that causes a decrease in bile salts, an increase in cholesterol, or a decrease in lecithin will create relative insolubility of cholesterol in solution.
 - d. It has also been shown that most patients with gallstones have a smaller pool of bile acid than matched controls without stones.

Stages in Cholesterol Gallstone Formation (Figure 1 and 2): *The three principal defects involved in gallstone formation are: cholesterol supersaturation, accelerated nucleation and gallbladder hypomotility.*

1. **Formation of cholesterol saturated bile:** The most critical factor is the ratio of cholesterol/bile acids. In general the likelihood of stone formation is increased by anything that raises cholesterol level or lowers bile acid levels, such as:
 - a. **Impaired bile salt return:** Seen with ileal disease (Crohn's), ileal resection or bypass. Drugs that bind bile acids in the gut, such as cholestyramine could also theoretically cause this problem, but new synthesis of bile acids by the liver usually suffices to compensate for the losses.
 - b. **Oversensitive feedback mechanism to turn off Cholesterol-7-hydroxylase,** the key regulatory enzyme in bile acid synthesis. Evidence for this is the existence of a group of

- gallstone patients who have a small bile acid pool but normal rate of bile acid synthesis.
- c. **Excessive cholesterol synthesis in the face of a normal bile acid pool.** HMG-CoA reductase, the rate-limiting step in cholesterol synthesis, is stimulated by insulin and food intake, both increased in obesity.
 - d. **Combination of mechanisms:** endogenous and exogenous estrogens appear to both increase cholesterol secretion and decrease chenodeoxycholate secretion. This is associated with estrogen treatment in women, Native American ethnic group, and the formation of gallstones in some patients with a lean body mass.
2. **Nucleation:** The next step in cholesterol gallstone formation is nucleation of cholesterol into crystals, followed by agglomeration of crystals and growth of the microlith into macroscopic gallstones. Normally in unsaturated bile, cholesterol is made soluble through association with bile salts and phospholipids (lecithin) forming vesicles (cholesterol and phospholipids alone) and micelles. As cholesterol saturation increases beyond the limits of vesicle and micelle formation cholesterol precipitates as crystals.

Nucleation promoters: Proteins exist in the gallbladder that promote or retard the nucleation of cholesterol crystals. Mucin glycoprotein is the most important pronucleator identified. At least five other proteins have been identified as putative nucleation promoters.
 3. **Growth:** The crystal acquires additional cholesterol to form a visible stone. Cholesterol stones often contain alternating layers of cholesterol crystals and mucoprotein. Pure cholesterol crystals are quite soft. Protein adds strength to the stone. This stage of stone formation is largely influenced by **gallbladder hypomotility** and stasis. Gallstones forming in patients with high spinal cord injury or treated with the somatostatin analog Octreotide have been largely associated with impaired gallbladder motility.
 4. **Gallbladder sludge**, or thickened gallbladder mucoprotein with tiny entrapped cholesterol crystals, is thought to be the precursor of gallstones. Sludge may also occur in asymptomatic patients with prolonged fasting or TPN, spinal cord injuries and prolonged treatment with octreotide. It can be seen on standard ultrasonography of the gallbladder. Sludge can sometimes cause biliary pain, cholecystitis, or acute pancreatitis, but may also resolve without treatment. The antibiotic ceftriaxone can precipitate in the gallbladder and bile ducts as sludge.

Risk Factors Associated with Cholesterol Gallstone Formation

Demographic	Drugs	Genetics
<ul style="list-style-type: none"> • Older age • Female Gender • Obesity • Weight Loss • TPN 	<ul style="list-style-type: none"> • Clofibrate • Oral Contraceptives • Estrogens • Progesterones • Ceftriaxone • Octreotide 	<ul style="list-style-type: none"> • Native Americans • Scandinavians <p>Ileal Diseases</p> <ul style="list-style-type: none"> • Crohn's Disease • Ileal resection

Bile Duct Stones

- A. **Primary bile duct stones** are stones formed in the biliary tree as the result of bile stasis, e.g. above a stricture, around foreign material such as a suture, or in association with infection. They are composed predominantly of calcium bilirubinate and minor amounts of cholesterol or fatty acids. These stones may be found in the intrahepatic or extrahepatic bile ducts.
- B. **Secondary bile duct stones** are found in the bile ducts in association with gallbladder stones, either having migrated out of the gallbladder or having formed concomitantly in the bile ducts. Their matrix reflects the composition of gallbladder stones, i.e. predominantly cholesterol in ~80%, and black pigment in ~20% of cases. Black pigment stones are usually idiopathic, but may be associated with chronic hemolysis or cirrhosis. Bacterial infection is not thought to be important in the pathogenesis of either type of

Clinical manifestations of gallstones

A. Asymptomatic gallstones:

1. 80% of people harboring gallstones are asymptomatic at any given point in time.
2. 20% of these patients will become symptomatic over a 10-15 year period.
3. Gallstones require no treatment until they become symptomatic. There are some exceptions:
 - a) patients with sickle cell anemia (symptoms of gallstones may mimic those of sickle cell crisis, and elective cholecystectomy is much safer than urgent operations in this group).
 - b) patients in remote locations where urgent medical care is not possible
 - c) patients with gallstones and calcification of the gallbladder wall, which is considered a premalignant condition (Porcelain Gallbladder).

B. Symptomatic gallstones need to be treated in a time frame that is appropriate for the seriousness of the clinical presentation, and the patient's general health. Recurrent biliary pain (or colic) is the most common indication for treatment.

C. Biliary Colic:

1. The *most common presenting symptom of cholelithiasis*.
2. The pain is a steady, severe aching or pressure-type sensation in the epigastrium or right upper quadrant, and often radiates to the infrascapular area or right scapula. The pain occurs suddenly and lasts about 1-3 hours.
3. It is thought that sudden transient obstruction of the cystic duct by a calculus produces increased intraluminal pressure and distention of the gallbladder, leading to this *visceral-type pain*.
4. Discrete attacks may be precipitated by meals, or may occur at any time of the day or night. The frequency of episodes may vary from weeks to years.
5. Nausea is common and vomiting occurs occasionally.
6. Laboratory tests usually are normal.
7. Recurrent pain attacks occur in up to 50% of patients and the risk of a more significant complication is estimated to be 1-2% a year.

D. Acute cholecystitis:

1. Results from *persistent obstruction of the cystic duct*, in contrast to the transient obstruction that produces biliary pain, results in acute cholecystitis.
2. Acute inflammation of the gallbladder is caused by calculous obstruction of the cystic duct in >90% of cases (some patients may present with *acalculous* cholecystitis).
3. Bacterial infection may supervene; enteric organisms have been cultured from 75% of patients with acute cholecystitis.
4. In contrast to biliary colic, acute cholecystitis causes a *parietal-type epigastric or right upper-quadrant pain* that increases with jarring or respiration. The patient prefers to remain motionless.
5. Inspiration during palpation of the right upper quadrant produces increased tenderness and inspiratory arrest (Murphy's sign). Tenderness in the scapular area (Boas' sign) is less common.
6. Nausea is common and vomiting occurs occasionally.
7. *Low grade fever and a leukocyte count of 10,000 to 15,000/mm³ with a shift to the left is usual. Liver enzymes may be elevated.*
8. In up to 75% of patients with acute cholecystitis, symptoms resolve spontaneously within 72 hours after onset, after the stone presumably disimpacts or passes through the cystic duct. In the remaining 25%, the inflammation progresses to necrosis, perforation or empyema of the gallbladder unless intervention occurs.
9. Clinical indications of progression are persistent symptoms signs of peritonitis, or rising temperature, pulse rate and white blood cell count. In elderly or diabetic patients or in patients treated with corticosteroids for other reasons, mild signs and symptoms may

10. When surgery is not performed, cholecystitis recurs in 25% of patients within the first year of follow-up and in 60% of patients within 6 years.
11. Complications of acute cholecystitis are empyema, an intraluminal gallbladder abscess from persistent complete obstruction of the cystic duct, gallbladder perforation (5%), often leading to a walled-off abscess.

Complications of gallstones:

1. Common bile duct obstruction from a gallstone may result, and may be partial or complete, continuous or intermittent. Choledocholithiasis occurs in 20% of patients with gallstones. Common bile duct stones may cause biliary type pain and elevated liver enzymes.
2. Ascending cholangitis: an infection with aerobic or anaerobic organisms, most frequently *E. coli*. due to common bile duct obstruction from a gallstone. *The classic clinical triad includes fever, pain and jaundice.*
3. Papillary stenosis: Scarring and stricturing of the ampulla caused by recurrent passage of stones through the ampullary orifice.
4. Choledocho-duodenal fistula: Formation of the fistulous tract between the bile duct and duodenum due to erosion of an impacted stone.
5. Gallstone ileus: A rare cause for small bowel obstruction when a large stone migrates from the common bile duct and impacts at the level of the ileocecal valve.
6. Acute pancreatitis: may occur as a result of ampullary obstruction by a gallstone (30%-75% of patients with acute pancreatitis have gallstones), or papillary stenosis.
7. Mirizzi's syndrome: When a gallstone in the cystic duct obstructs the common bile duct by extrinsic compression
8. Surgical complications: may lead to *biliary strictures, bile leaks, or transection of the bile ducts.*
9. Gallbladder cancer: accounts for one third to one half of gallstone related death in USA. About 80% of patients with gallbladder cancer have stones, and 1% of patients with gallstones at autopsy have gallbladder cancer. Patients with symptomatic stones develop gallbladder cancer at higher rates than do patients with asymptomatic stones. Gallbladder cancer occurs in 50% of patients with a calcified gallbladder wall (porcelain gallbladder), and in 3-5% of Native Americans, particularly if they have gallstones.

Diagnosis

1. Plain abdominal x-ray - 20% of gallstones visualize (>4% calcium by weight). Cholesterol gallstones are radiolucent.
2. Ultrasonography – The initial imaging test for gallstones. In addition to the presence of gallstones, ultrasonography can detect signs of acute cholecystitis (gallbladder wall thickening, pericholecystic fluid), and give information regarding the bile ducts (dilation, presence of stones).
3. Hepatobiliary scan (HIDA) - relies upon hepatic uptake and excretion into bile of an IV radioactive compound. Images of the biliary tree are recorded by a gamma camera. Reliable study of obstruction (e.g. obstructed cystic duct: no contrast seen in gallbladder. Obstructed common bile duct: no contrast seen in duodenum, etc.), and of gallbladder muscular function (gallbladder ejection fraction can be measured after CCK injection). Can be done and is diagnostic in patients with acute cholecystitis.
4. Endoscopic Ultrasound: Can detect gallbladder and common bile duct stones and has been used in patients with gallbladder type symptoms and negative ultrasound and HIDA scans.
5. MRI/MRCP: an excellent imaging modality to assess for common bile duct stones.

Treatment modalities for gallstone disease

Surgical removal of the gallbladder is the standard treatment for patients with recurrent biliary colic and acute cholecystitis. The patient should initially be stabilized with antibiotics and fluids to reduce anesthesia complications. Unstable patients should be managed percutaneously, initially for drainage of bile alone, later for elective stone extraction. Patients with concomitant cholangitis (infection of the bile ducts) should undergo initial endoscopic or percutaneous drainage, irrespective of age, as operative mortality is exceedingly high in the phase of acute cholangitis, and antibiotics alone are not sufficient to treat the infection in the setting of persistent biliary obstruction.

Non-surgical treatment modalities have their best application in patients in whom surgical management would not be prudent, because of age or concomitant medical illness.

Therapy

A. Dissolution Therapy

1. *Oral Agents:* Oral intake of ursodeoxycholic acid (Ursodiol, *Actigall*), reduces biliary output of cholesterol. Ursodiol is a naturally occurring bile acid. Ursodiol reduces the synthesis of cholesterol in the liver and its secretion into bile, without inhibiting synthesis of endogenous bile acids. It causes a competitive blockade of bile acid reabsorption in the terminal ileum. Its multiple effects cause cholesterol desaturation in bile without raising serum cholesterol levels. Ursodiol also prolongs the nucleation time in the gallbladder bile by shifting cholesterol from vesicles to micelles. *Therapy with bile acids is suitable only for a minority of patients who refuse or are poor risk for surgery. It has no place in the management of acute cholecystitis.*
2. Cholesterol gallstones dissolve at the rate of about 1 mm per month and disappear completely within 6-24 months in only 30-50% of patients. Success is increased by strict patient selection, and is greater for small pure cholesterol gallstones. Ursodiol should not be used for calcified gallstones or if the cystic duct is obstructed. Ursodiol has been used to prevent gallstone formation in patients undergoing weight reduction.
3. *Contact Agents:* Methyl-tert-butyl ether (MTBE) can dissolve cholesterol gallstones within 24 hours. It requires direct instillation into the gallbladder either endoscopically or percutaneously. It is rarely used. Monoctanoin, another contact dissolution agent, has been available for a long time, but its efficacy is very low.
4. *Gallstone recurrence and prevention:* The potential for gallstone recurrence exists in all patients treated with modalities that leave the gallbladder in place. Gallstones will recur in ~50% of the subjects within 5-7 years from successful dissolution. The potential for recurrence should not preclude dissolution in poor surgical candidates with limited life expectancy. Prevention of gallstone recurrence with oral bile acids is effective, but expensive.

B. Biliary Extracorporeal Shock Wave Lithotripsy uses high amplitude sound waves to fragment stones like with kidney stones. In the 1980's Thomas Jefferson Hospital was one of the first hospitals in the country to utilize this technology. The machine now sits idle in a basement somewhere collecting dust. The low efficiency, added to the high cost and high recurrence rates (11.5% 1.5 years after complete clearance) have made the use of extracorporeal biliary lithotripsy obsolete in this country.

C. Laparoscopic cholecystectomy. Is the standard surgical technique for removal of the gallbladder via a laparoscope inserted through a small incision in the umbilicus. Surgical instruments are inserted through stab wounds in the upper abdomen. Compared to open cholecystectomy, it requires reduced hospital stay and recuperation time. Postoperative pain is significantly reduced, and surgical scars are less visible. Patients are usually discharged the day after the operation, and are able to return to work in only 1-2 weeks. Extensive abdominal scarring, unfavorable anatomy, or a complication may require conversion of planned laparoscopic cholecystectomy into an open operation. Compared to the open operation, laparoscopic cholecystectomy requires more O.R. time, and perhaps higher surgical skill. Complications may be slightly more frequent with the laparoscopic operation,

and tend to occur early in the surgeon's laparoscopic experience.

Laparoscopic removal of common bile duct stones through the cystic duct is available at many centers. It requires added surgical skill and significant additional anesthesia time. When the surgeon detects bile duct stones by cholangiography *during* cholecystectomy, he or she may attempt to remove them translaparoscopically through the cystic duct if possible (depending on training of the surgeon, availability of equipment necessary, size of the stones, and anatomy of the cystic duct). The surgical alternatives are to convert the operation to open, and perform common bile duct exploration, or to complete the cholecystectomy laparoscopically and use postoperative ERCP to clear the bile ducts. If the bile duct stones are known to be present *before* cholecystectomy, their clearance with ERCP is usually performed preoperatively, and laparoscopic cholecystectomy is scheduled to follow, or the patient can be managed directly with open cholecystectomy and common bile exploration.

- D. Endoscopic Therapy.** Endoscopic retrograde cholangiography (ERCP) has significantly reduced the need for surgical exploration in patients with common bile duct stones. If stones are found, an electrocautery cutting instrument can be inserted into the ampulla to enlarge the opening of the bile duct into the duodenum (sphincterotomy). Stones can consequently be removed by means of balloons or baskets. ERCP with sphincterotomy is the treatment of choice for retained or new bile duct stones after cholecystectomy. ERCP/sphincterotomy *not followed* by cholecystectomy is used to treat bile duct stones in patients who are poor risks for surgery and who have concomitant gallbladder stones without cholecystitis. Patients who will later develop cholecystitis can be treated percutaneously, and still avoid general anesthesia.
- E. Percutaneous Therapy.** Percutaneous access, traditionally offered by Interventional radiologists, is used to treat both gallbladder and bile duct stones. In addition to drainage of infected bile, it allows fragmentation or dissolution of stones. Needle tracts can be dilated to allow passage of thin cholangioscopes with operating channels. Combined efforts with gastrointestinal endoscopists have been used to avoid operations in poor surgical candidates.
- F. Transgastric endoscopic cholecystectomy:** Believe it or not endoscopic researchers are developing a technique where an endoscope is inserted through the mouth into the stomach and then through a puncture site in the stomach it is advanced intraperitoneally. Cholecystectomy is then performed endoscopically and the gallbladder is pulled through the stomach and the puncture site is then sealed endoscopically. This may be the future for non-invasive endoscopic cholecystectomy. Remember you heard it hear first.

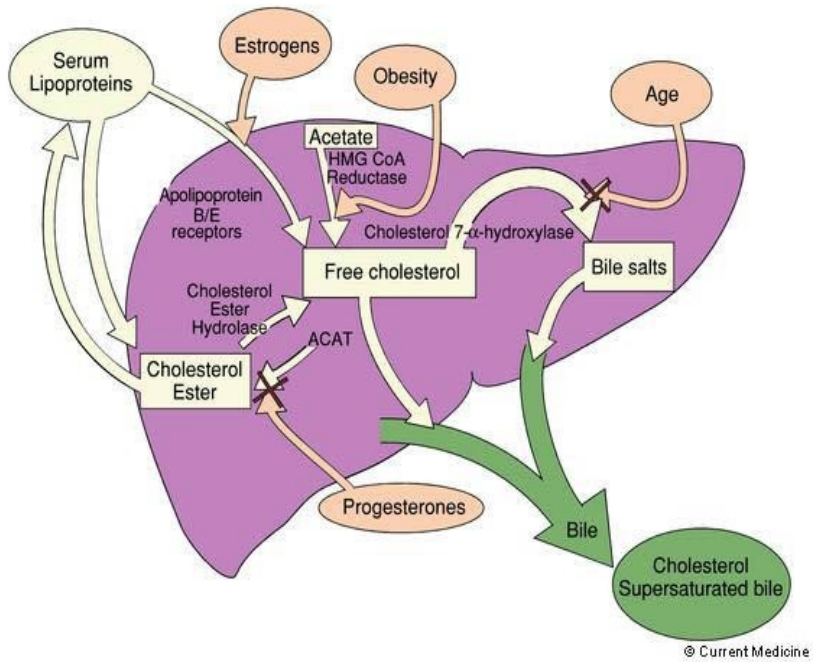
Suggested Reading

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Cholesterol hypersecretion



Gallbladder events in cholesterol gallstone formation

