

CHOLELITHIASIS – Gallstone Disease

Introduction

Cholelithiasis – gallstone disease – is a very common medical malady. There are over 700,000 cholecystectomies (removal of the gallbladder) performed in the United States each year,¹ and it has been estimated that at any given time, at least 25 million people in the United States have gallstones.² Complications are not common and mortality from the disease is very, very low. There are risk factors that increase the chances of developing gallstones– e.g., gender, age, and genetic traits – that cannot be changed, but there are many lifestyle risk factors, as well.³ Treatment focuses on altering these lifestyle factors, the use of medications, or surgery.⁴

When the student has finished this module, he/she will be able to:

1. Identify two functions of bile.
2. Identify two reasons for the formation of gallstones.
3. Identify two lifestyle risk factors for the development of gallstones.
4. Identify the three of the most common complications of gallstone disease.
5. Identify a drug that can be used for gallstone disease.

Anatomy and Physiology of the Biliary System

Gallstones are formed in the *biliary* system. The biliary system is concerned with the production, storage and secretion into the gut of *bile*, and it is comprised of the liver, the gallbladder, and the biliary tract.

- The *liver* is located in the right upper quadrant of the abdomen. The liver has many functions: synthesis, storage and breakdown of glycogen, synthesis of clotting factors, storage of blood, manufacture and breakdown of hormones, synthesis of bile salts needed for absorption of fat-soluble vitamins and lipids and removal of cholesterol., metabolism, detoxification and removal of endogenous and exogenous compounds, metabolism and removal of drugs, and *bile formation*. The basic unit of the liver is the *hepatocyte* (hepato is a prefix that refers to the liver). The hepatocyte can be thought of as having two distinct ends: the basolateral membrane that faces the blood vessels of the liver and the apical membrane that faces the bile *canaliculi* (Latin for canal). The canaliculi collect the bile that is secreted by the hepatocytes, directs it into the *terminal bile ducts* and from there the bile flows into the *hepatic ducts*, into the *common bile duct* and into the gallbladder where it is stored before it is released into the small intestine.
- The *gallbladder* is a small, muscular sac that is nestled into the liver. Its primary function is to concentrate and store bile. The gall bladder is connected to the common bile duct (at about the same place that the hepatic ducts join the common bile duct) by the cystic duct. Bile is stored in the gallbladder until it is needed for the digestion of fat in the gut. Fat entering the small intestine causes the release of

a hormone called *cholecystokinin* from the intestinal mucosa. Cholecystokinin is absorbed into the blood stream, reaches the gallbladder and stimulates it to contract and empty bile into the small intestine (cholecystokinin also relaxes the *sphincter of Oddi*, the sphincter at the junction of the bile duct and the small intestine). The gallbladder also acts to determine the final composition of bile by absorbing water, sodium chloride and other electrolytes and leaving behind bile that is concentrated with bile salts, cholesterol and bilirubin. Although the liver produces between 700 and 1200 milliliters of bile in a 24-hour period, the gallbladder can only store 40 to 70 milliliters, but due to the concentration of the bile by the gallbladder, that is enough.

- The *biliary tract* is the system of channels through which bile flows. It consists of the bile canaliculi, terminal bile ducts, right and left hepatic ducts in the liver; the cystic duct that goes from the gallbladder to the common bile duct; and the common bile duct that carries bile (along with pancreatic secretions; before the common bile duct enters the small intestine, there is an anastomosis with the pancreatic duct) through the sphincter of Oddi into the small intestine.⁵

What is Bile?

Bile is a yellow-green, alkaline fluid secreted by the hepatocytes. The basic components of bile are cholesterol, phospholipids, bilirubin and bile salts (there are other, less important components as well). Bile performs two basic functions: it helps the body digest fats, and it acts as an important excretory pathway for endogenous substances (e.g., cholesterol) and exogenous substances (e.g., drug metabolites). Bile digests fats by using the detergent action of the bile salts to break down fat globules into small sizes. When the fat molecules have been reduced, this enables the digestive enzymes to act on the surface of the fat and break them down further so they can be absorbed; this process is called *emulsification*. Bile is also an excretory pathway for drugs and toxins that are metabolized by the liver and that cannot be excreted by the kidney.

How is Bile Formed?

The basic unit of the liver, the hepatocyte, has two surfaces. The basolateral membrane faces the liver sinusoids and is in contact with hepatic blood flow. Substances in the hepatic blood – cholesterol, drug metabolites, bile salts, toxins, etc – are transported from the liver's blood flow into the hepatocyte by osmotic pressure, hydrostatic forces, and by active, energy-dependent transport molecules. Once inside the hepatocytes, these compounds are changed to allow for their excretion via bile into the hepatic canaliculi through the apical membrane (this is the side of the hepatocyte that faces the bile canaliculi of the hepatocyte) and bile is formed. Osmotic pressure and active transport (through an ATP-dependent pump) secret the components of bile into the canaliculi. Bile is further concentrated by the epithelial cells lining the bile duct and concentrated again by the gallbladder.⁶

Gallstone Formation

Gallstones are classified as either cholesterol stones or pigment stones.⁷

Cholesterol stones are more common; they account for approximately 75%-80% of all cases of cholelithiasis in the United States.⁸ There are three reasons for the formation of cholesterol gallstones:

- Cholesterol supersaturation of bile: Bile acids and phospholipids normally help keep cholesterol soluble so that it does not precipitate out. However, there are times when the ratio of bile acid and phospholipids to cholesterol in the bile is altered, the bile becomes supersaturated with cholesterol, and it crystallizes into cholesterol gallstones. This can happen when there is hypersecretion of cholesterol into bile by the liver (the most common cause) or hyposecretion of bile salts or phospholipids.⁹
- Gallbladder hypomotility: Even if the bile is supersaturated with cholesterol, gallstones will not form if the bile is emptied from the gallbladder in a normal amount of time. Hypomotility of the gallbladder may be caused by excess cholesterol in the bile. This affects the function of the smooth muscle of the gallbladder and inhibits its contraction.¹⁰
- Nucleation of cholesterol monohydrate crystals: Nucleation is a process by which crystals in the bile gather together in large enough amounts to form a stone. It is not clear why this happens, but it may be that there is an imbalance between glycoproteins that accelerate and enhance this process and glycoproteins that inhibit the process.^{11,12}

Pigment stones are classified as either black or brown.¹³ Black pigment stones are primarily comprised of calcium bilirubinate. Brown pigment stones are comprised of calcium salts of unconjugated bilirubin, bile salts, cholesterol, and fatty acids. Black stones are caused by a variety of pathologies. Hemolytic anemias (e.g., sickle cell disease) cystic fibrosis, and B₁₂ or folic acid deficiencies cause an excess of unconjugated bilirubin. Crohn's disease increases the bilirubin load in the gut and causes it to crystallize out.¹⁴ Brown pigment stones are caused by an infection in the gallbladder that results in a decrease in the solubility of unconjugated bilirubin.¹⁵

Learning Break: *Bilirubin* is a cellular antioxidant that is found in the heme portion of hemoglobin. When red blood cells break down, bilirubin is released from the heme as *unconjugated bilirubin*. It is transported to the liver, joined (conjugated) with glucuronic acid (an acid that binds with xenobiotics and toxins so they can be eliminated) and now, as *conjugated bilirubin*, excreted in the bile.

PREDETERMINED RISK FACTORS FOR CHOLELITHIASIS

The predetermined risk factors for cholelithiasis are certain medical conditions, gender, ethnicity, inherited susceptibility, and age.¹⁶

- Age: For women, the risk of developing gallstones after the age of 15 increases by approximately 1% a year; for men, the risk increases approximately 0.5% per year.¹⁷ Cholelithiasis is almost unknown in children.

- Gender: Gallstones are more common in women. Young women have a much higher risk than young men; in later decades, the risk for men increases but never equals that of women.¹⁸ Pregnant women have a higher risk than women who are not pregnant. This, along with the gender difference, is thought to be caused by estrogen and progesterone; progesterone may cause pooling of the bile in the gallbladder and estrogen increases the concentration of cholesterol in bile.^{19,20}
- Genetics: There is no doubt that a predisposition to forming gallstones can be inherited.²¹ It has been estimated that this genetic susceptibility accounts for approximately 30% of the population's risk for developing gallstones.²²
- Ethnicity: Gallstones are common in Europe, North America, and South America, but are uncommon in Asia and Africa.²³
- Medical conditions: Medical conditions that increase the risk for developing gallstones include cirrhosis, Crohn's disease, irritable bowel syndrome, hemolytic anemias, cystic fibrosis, B₁₂ or folic acid deficiency, and spinal cord injury.^{24,25}

Modifiable Risk factors for Cholelithiasis

- Obesity: Obesity is a well established risk factor for the development of cholelithiasis, especially for women.^{26,27,28} People who are obese have increased concentration of cholesterol in their bile.²⁹
- Diet: There is some evidence that diet – particularly a diet high in fat - may increase the risk of developing gallstones, but there is no conclusive proof that diet can increase or decrease the risk for developing cholelithiasis.³⁰ Although most gallstones are comprised of cholesterol, a high serum cholesterol has not been associated with an increased risk for gallstone disease.³¹
- Rapid weight loss: A low calorie diet and rapid weight loss (causing a release of cholesterol from the tissues and increasing the cholesterol concentration of the bile) is a major risk factor for cholelithiasis; bariatric surgery is, as well.^{32,33}
- Drugs: Ceftriaxone (a cephalosporin antibiotic), octreotide (used for treating acromegaly, complications of carcinoid syndrome, and certain cancers), clofibrate (used for lowering serum cholesterol and triglycerides) and estrogens may increase the risk of developing gallstones.³⁴ Total parenteral nutrition increases this risk, as well.³⁵
- Sedentary lifestyle: A sedentary lifestyle may increase the risk for developing gallstones.³⁶

Signs and Symptoms of Cholelithiasis

Most people who have gallstones have no complaints and are not aware they have the disease.³⁷ Signs and symptoms are caused by inflammation, or obstruction if a stone moves into the common bile duct or the cystic duct; the gallbladder contracts to release bile, and the blockage caused by the stone causes the pain.³⁸ *The patient usually experiences a steady, often severe pain in the right upper quadrant or the epigastric area.* The pain is referred to as *biliary colic*. It may radiate to the right shoulder or the back (this is called Collin's sign).³⁹ It often starts within an hour after a meal and typically lasts

from 1 to 5 hours. *Nausea and vomiting are common*; a fever indicates a complication, e.g., cholecystitis, cholangitis, or pancreatitis.⁴⁰

Learning Break: Gallstones are very common, but the risk of developing symptoms or complications is very low. One study of men with gallstones found that 10% of all patients with the disease developed symptoms after 5 years and 18% developed symptoms after 15 years.⁴¹

Diagnosing Cholelithiasis

Aside from the signs and symptoms mentioned above, ultrasound of the gallbladder will reveal the stones, and the procedure as a diagnostic tool is very specific and sensitive.⁴² Ordinary x-rays are not useful. Laboratory studies will be normal unless the patient has an obstructive, infectious, or inflammatory process.⁴³

Learning Break: There are many pathologies that can present with signs and symptoms similar to an episode of biliary colic, and a simple case of gallstones needs to be distinguished from one of the complications, e.g., acute cholecystitis. *The patient with biliary colic and no complications will have pain that is not localized, will not have a fever, and will not have rebound or guarding.*⁴⁴

MORBIDITY, MORTALITY, AND COMPLICATIONS

Morbidity and mortality from gallstones is very low. The average risk of developing symptoms is approximately 2.0-2.6% a year.⁴⁵ The risk for complications is also slight, perhaps 0.5% to 3% a year.⁴⁶ Cholelithiasis causes approximately 10,000 deaths a year in the United States.⁴⁷ Most of these (75%) are due to pancreatitis, and the majority of the others are due to gallbladder cancer.⁴⁸

Learning Break: Once the patient becomes symptomatic, the risk of complications rises sharply.⁴⁹

The most common complications of cholelithiasis are **cholecystitis, cholangitis, pancreatitis, and gallbladder cancer.**

Learning break: There are other complications of gallstone disease such as the Mirizzi syndrome, gallstone ileus, and fistulas, but these are very uncommon.

Cholecystitis

Cholecystitis is an acute inflammation of the gallbladder. When it involves gallstones (90% of all cases) it is caused by impaction of a stone in the neck of the gallbladder, the cystic duct, or Hartmann's pouch (Hartmann's pouch is an abnormal sac that is sometimes seen in the neck of the gallbladder).⁵⁰ Bile flow is obstructed, and patients experience nausea, vomiting, pain, and fever.

Learning Break: Cholecystitis can be distinguished from biliary colic by the prolonged duration of the pain and the presence of *Murphy's sign*.⁵¹ As the right upper quadrant is palpated, the patient is asked to breath in; if the patient has cholecystitis, he/she will not be able to completely inhale. Murphy's sign is considered to be highly sensitive and predictive.

Cholangitis

Cholangitis is inflammation and infection of the biliary tract. It is caused by a bacterial infection and obstruction of the biliary tree; the obstruction is most often due to a gallstone.⁵² Cholangitis is characterized by Charcot's triad of fever, right upper quadrant pain, and jaundice.⁵³ It is a very dangerous pathology; mortality rates can be 100% if patients are not properly treated and do not respond to conservative therapy.⁵⁴

Pancreatitis

Gallstones can move into and obstruct the distal common bile duct. When this occurs, bile and duodenal contents can reflux into the pancreatic duct and cause pancreatitis.⁵⁵ It is a relatively common disorder: it has been estimated that 80% of all cases of pancreatitis are caused by alcohol abuse or gallstones and of that 80%, 30% to 75% are due to gallstones.⁵⁶ Most patients present with nausea, vomiting, and severe epigastric pain that radiates to the back. The majority (approximately 75%) of all cases of gallstone pancreatitis are mild, but severe complications such as necrosis and abscess formation can be seen.⁵⁷

Gallbladder Cancer

Gallstones increase the risk of developing gallbladder cancer by 4-5 fold.⁵⁸ Gallbladder cancer is not a common cancer, but these tumors account for a significant number of the deaths that are attributed each year to cholelithiasis. The five-year survival rate is low – approximately 15% to 20%. Although there are, possibly, many factors that involved in the pathogenesis of gallbladder cancer, chronic inflammation caused by gallstones is probably the most important.⁵⁹

TREATMENT

Treatment for cholelithiasis can involve medications, lifestyle changes, or most commonly, surgery.

Medications

Ursodeoxycholic acid (UCDA) can be used to dissolve gallstones and to prevent gallstones from forming. It acts by decreasing cholesterol saturation of bile. It may also decrease crystal nucleation and decrease the cholesterol content of gallstones.⁶⁰ Unfortunately, the drug is very expensive, it must be taken for several years, and gallstones recur in approximately 30% to 50% of all patients treated with UCDA.⁶¹ The

drug is most often used for patients who do not want or cannot tolerate surgery, or for patients who develop choledocholithiasis (stones in the common bile duct) after gallbladder surgery.⁶²

Learning Break: At one time, shock wave therapy of gallstones – lithotripsy – was considered a promising treatment for cholelithiasis and was relatively popular. This technique was effective if the stones were small and not dense. But if there were multiple stones or the stones were large (> 16 mm) it did not work well. Also, it was difficult to predict which patients which respond well to lithotripsy and the recurrence rate was unacceptably high.⁶³ This therapeutic approach to the disease has been abandoned.⁶⁴

Learning Break: There is some strong evidence that non-steroidal anti-inflammatory drugs can reduce the risk of developing cholecystitis in patients with symptomatic gallstone disease.⁶⁵

Lifestyle Changes

There no *conclusive* evidence that dietary modifications and/or changes in an individual's level of physical activity could prevent the formation of gallstones.⁶⁶ Research has suggested that a diet high in fiber, high in consumption of nuts, and low in consumption of saturated fatty acids and trans-fatty acids may be preventative, but the studies have been limited in scope.^{67,68,69} Moderate exercise⁷⁰ and moderate weight loss⁷¹ may prevent gallstone disease.

Surgery

Most cases of cholelithiasis are asymptomatic, and treatment for these patients is not recommended.⁷² However, in certain circumstances, elective removal of the gallbladder needs to be done:^{73,74}

- Children who have gallstones.
- Gallstones greater than 2 centimeters in diameter.
- People who are at an increased risk for gallbladder cancer.
- People with a calcified (“porcelain”), non-functional gallbladder.
- People who are having surgery for obesity and have preexisting gallstones are considered to be candidates for prophylactic gallbladder surgery.
- Patients with sickle cell anemia (it can be difficult to distinguish between biliary colic and a sickle cell crisis).
- Patients with spinal cord injuries or neurological conditions affecting pain pathways in the abdomen.

Removal of the gallbladder is recommended for patients with symptomatic gallstone disease.⁷⁵ There are three techniques that can be used:⁷⁶

- Open cholecystectomy: Also known as traditional open cholecystectomy. A large abdominal incision is made and the gallbladder is retracted and then removed.

- Small-incision cholecystectomy: The surgeon uses an abdominal incision, but it is 6 to 8 cm long.
- Laparoscopic cholecystectomy: This is now considered to be the standard approach and it is safer than the open techniques. Four trocars are placed in the peritoneal cavity; one is used for the camera, the others are used for performing the procedure. Recovery time and operative time are much less than the other techniques, the rate of complications is less than that of the open techniques, and the procedure can often be done as outpatient day surgery. The biggest risk is damage to the common bile duct. This complication happens more often with the laparoscopic technique than the open techniques, but it is not common; it occurs in approximately 0.2% to 0.5% of all cases.⁷⁷ Prophylactic antibiotics are not used unless there is a high risk of post-operative infection.⁷⁸ It appears that the sooner the procedure is performed, the better the success rate and the fewer complications that occur.⁷⁹

Learning Break: Laparoscopic cholecystectomy has been shown to be very safe. The mortality rate associated with the procedure is essentially zero, and the rate of serious complications is also very low.^{80,81} The intra-operative and postoperative risks are increased in patients over the age of 70, in patients with poor baseline health status, and in patients with complicated gallstone disease.⁸²

Learning Break: Injury to the common bile duct that occurs during laparoscopic cholecystectomy can be mild, easily repaired, and well tolerated. But this iatrogenic damage has also been found to seriously damage quality of life⁸³ and decrease survival rate.⁸⁴

Learning Break: Some surgeons have successfully used an approach called “*the critical view of safety*” (CVS) approach and have found it decreases bile duct injuries. In this technique, Calot’s triangle (an anatomic space bordered by the cystic artery, the cystic duct, and the hepatic duct) is cleared of fat and fibrous tissue and the gallbladder is removed from the lowest part of its attachment to the cystic bed. In this way, the bile duct is more easily seen and inadvertent injury can be avoided.⁸⁵

POST-OPERATIVE COURSE

Most patients (approximately 70% to 95%) have complete relief of symptoms after cholecystectomy.⁸⁶ About 5% to 10% develop chronic diarrhea, but this is usually mild and over the counter medications are usually sufficient to manage this problem.⁸⁷ No special diet is required.

Approximately 10% to 15% of all patients who have had a cholecystectomy experience *postcholecystectomy syndrome*.⁸⁸ There are many possible causes, and the signs and symptoms are probably due to increased bile flow into the upper gastrointestinal tract – which can cause esophagitis and gastritis – and bile flow into the lower gastrointestinal tract – which can cause colicky pain and diarrhea.

LAPAROSCOPIC CHOLECYSTECTOMY: PATIENT EDUCATION

- If you have been diagnosed with gallstones, notify or see your doctor immediately if you have abdominal pain and you *also* have fever, chills, vomiting, or chills. These are indications that you may have a serious complication.
- The procedure is safe and effective, and serious complications are unusual.
- The procedure is done using general anesthesia.
- It takes approximately 20 minutes to 60 minutes to complete.
- Recovery time differs, but most people go home the same day.
- Occasionally your surgeon may decide to perform a procedure called *endoscopic retrograde cholangiopancreatography* (ERCP) before removing your gallbladder. This procedure uses a special scope (an endoscope) to look for and remove gallstones that have moved out of the gallbladder.
- Some pain is normal after the procedure, but it usually lasts only a day or so. You may have diarrhea, as well, but this is not common and is usually mild.
- Most people can resume all of their normal activities in a week or two after the surgery. You can eat whatever you like and whatever you can tolerate.

SUMMARY

Gallstones are one of the most common medical problems in the United States. Gallstones are usually comprised of cholesterol, but there are also pigment stones – black and brown. Advanced age, obesity, female gender, and pregnancy are the biggest risk factors for developing gallstones; the tendency to form gallstones is also, in part, inherited. Some drugs and some disease states can also cause gallstones, and there is some evidence that diet and activity level may play a part, as well. The most effective diagnostic tool for determining the presence of gallstone is ultrasound.

Most people do not have symptoms, and for them prophylactic cholecystectomy is not recommended unless the patient is very young or has certain medical conditions. For people with gallstones who experience persistent pain, the risk of complications, e.g., cholecystitis, cholangitis, pancreatitis, etc., is increased. For them, surgery is recommended and laparoscopic cholecystectomy is the procedure of choice. It is safe, the mortality rate is essentially zero, and complications are unusual. Bile duct injury is the most serious complication of this procedure. The drug UCDA can be used for some patients to dissolve gallstones, but this is not a popular treatment. Lithotripsy was used at one time, but is no longer considered to be effective. Most people are symptom-free after the operation and resume their normal diet and activities.

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