

Gallstones

Causes, diagnosis and treatment

THOMAS J. HUGH MD, FRACS

Laparoscopic cholecystectomy is the treatment of choice for symptomatic gallstones. It should also be considered for selected patients with asymptomatic gallstones.

Key points

- Gallstones are common in Western populations.
- Risk factors for gallstones include female sex, older age, diabetes and obesity.
- Typical gallstone symptoms include upper abdominal or right upper quadrant pain (biliary colic), bloating and low-grade nausea.
- Complications of gallstones include acute cholecystitis, cholangitis and acute pancreatitis.
- Abdominal ultrasound examination has the highest sensitivity and specificity of any investigation for diagnosing gallstones.
- Laparoscopic cholecystectomy is a safe, effective treatment for symptomatic gallstones and may be considered for selected patients with asymptomatic gallstones.

Gallstones cause significant morbidity in Western societies. Symptomatic attacks requiring hospital admission have a major economic impact in terms of lost working days and costs to the overall health budget. In Australia, more than 50,000 cholecystectomies are performed annually.¹ With the advent of laparoscopic cholecystectomy in the early 1990s, the number of elective cholecystectomies increased as patients sought the benefits of minimal postoperative pain and early recovery compared with an open operation. This article discusses the causes, presenting symptoms, investigations and management options for patients with gallstones. Terms used to describe biliary symptoms and pathology are also precisely defined as these are frequently misused in the medical literature.

WHAT ARE GALLSTONES AND WHY DO THEY FORM?

There are three types of gallstone: cholesterol stones, pigment stones and 'mixed' stones (Figures 1a to d). Most gallstones (80%) in patients from Western societies are made up of cholesterol.

Supersaturation of the bile with cholesterol or a reduction in bile salts are thought to lead to gallstone formation (cholelithiasis). Both sexes may be affected, but gallstones are more common in women. The best predictors of the presence of

gallstones are older age and a history of biliary colic in both sexes, followed by diabetes in men, and obesity and higher number of pregnancies in women.² The old adage that the 'five Fs' summarise the causes of gallstones (fair, fat, forty, fecund and female) is a generalisation. The most common risk factors for gallstones are as follows.³

- **Sex.** Women are twice as likely to develop gallstones as men, which is thought to be due to higher levels of oestrogen, particularly during pregnancy or with use of hormone replacement therapy or the oral contraceptive pill.
- **Family history.** Although a specific gene has not been identified, close relatives often have known gallstones or have undergone cholecystectomy.
- **Weight.** Even moderately overweight patients have an increased risk of developing gallstones compared with normal-weight patients. This is attributed to reduced production or gut absorption of bile salts, leading to a relative increase in cholesterol saturation of bile.
- **Diet.** Patients who consume a diet high in fat and cholesterol have an increased risk of gallstones compared with those who consume lower fat diets. However, this risk is not directly related to serum cholesterol level.

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Figures 1a to d. Examples of gallstones. a (top left). Large mixed gallstones containing cholesterol and pigment. b (top right). Small mixed gallstones. c (bottom left). Multiple small cholesterol gallstones. d (bottom right). Gallbladder with small pigmented gallstones.

- **Rapid weight loss.** This results in secretion of higher levels of cholesterol into the bile. This leads in turn to supersaturation of bile within the gallbladder resulting in the formation of stones.
- **Age.** Patients over the age of 60 years have a higher risk of gallstone formation than younger patients.
- **Diabetes.** Patients with type 1 or 2 diabetes have high blood levels of fatty acids (particularly triglycerides), which are thought to increase the risk of gallstones.
- **Ethnicity.** Indigenous South American people have the highest risk of developing gallstones compared with any other race. The exact gene or genes responsible for this predisposition are unknown.

GALLSTONE SYMPTOMS

Biliary pain is caused by stones blocking either the cystic duct draining the

gallbladder or the main bile duct draining from the liver (the common hepatic or common bile duct). Prolonged obstruction causes secondary infection of the gallbladder wall, leading to acute cholecystitis. Stones may also pass into the extrahepatic biliary tree (choledocholithiasis; Figures 2a and b). Secondary infection due to obstruction of the biliary tree results in cholangitis, while passage of a stone through the distal common bile duct may cause pancreatitis.

The term 'biliary colic' refers to the pain experienced with uncomplicated gallstones. In fact, this term is a misnomer because the pain is usually constant in nature rather than cramping or colicky as occurs in the gut. The origin of the pain is not fully understood but, in part, may be caused by contraction of the smooth muscle wall of the gallbladder against an obstructing stone in the cystic duct. The pain often comes on after eating a fatty or 'heavy' meal, although

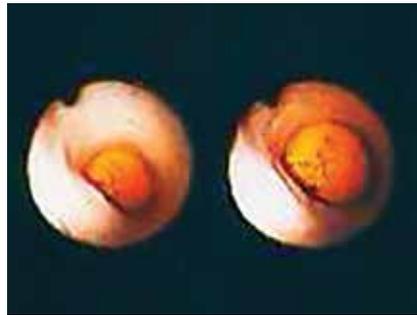
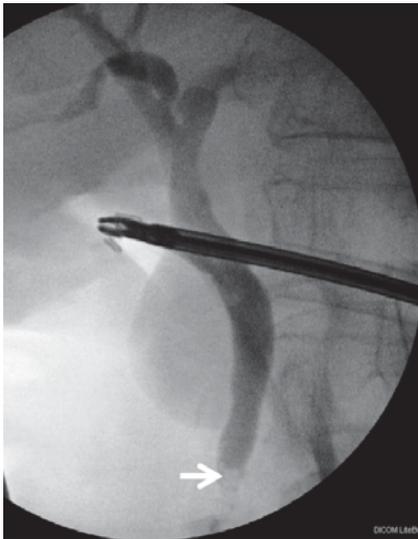
it can also develop without an obvious precipitating cause. The fact that patients often wake with pain in the early hours of the morning suggests gallbladder activity as the previous night's meal is digested. Anecdotally, lamb and pork are often implicated as precipitators of biliary colic, presumably because of the relatively high fat content of these meats.

Gallstone pain is often described as 'band-like' or a 'tight feeling' across the upper abdomen. Some patients experience a constant ache below the right rib cage. Occasionally, the pain may radiate through to the interscapular region or to the right shoulder. There may be associated nausea, dry retching or vomiting. In uncomplicated biliary colic, these symptoms usually resolve after several hours or after a protracted bout of vomiting. Symptoms that do not settle spontaneously suggest the development of complications such as cholecystitis, cholangitis or pancreatitis. When a stone passes into the extrahepatic biliary tree, jaundice may develop; often the first sign the patient notices is 'tea-coloured' urine.

Most patients with typical biliary colic do not have a significant alteration in their bowel habit. Occasionally, however, they have a history of fatty food intolerance, with loose, frequent stools or undigested food in the stools after fatty meals. It is important in these patients to take a careful history to exclude a primary small or large bowel problem that might be responsible for these symptoms.

Atypical or unusual biliary symptoms

Some patients present with atypical pain or may have other symptoms predominating, such as anorexia, nausea, abdominal bloating or vomiting. These symptoms may be precipitated by fatty foods, which is a clue that they are biliary in origin. In clinical practice, approximately 20% of patients describe a high epigastric or retrosternal 'discomfort' that may be difficult to differentiate from oesophageal spasm or cardiac pain. In other patients, the predominant symptom may be 'reflux' or 'heartburn'. Low-grade nausea or



Figures 2a and b. Choledocholithiasis. a (left). Intraoperative cholangiography showing a stone in the distal common bile duct (CBD; white arrow). b (above). Choledochoscopy showing a stone obstructing the distal CBD.



Figure 3. Ultrasound image of the gallbladder showing a large gallstone.

anorexia may be the only symptoms in those with a chronically inflamed gallbladder. Left-sided abdominal or shoulder pain are uncommon symptoms of gallstones, and other pathologies should be considered in patients with this symptom.

COMPLICATIONS OF GALLSTONES

Acute cholecystitis

Repeated attacks of biliary colic may eventually develop into acute cholecystitis. It is not clear why acute cholecystitis develops in only some patients. It may occur with both small and large gallstones but appears more common in patients with large stones, presumably as a result of obstruction of the cystic duct. A severe and prolonged infection may lead to a localised liver abscess adjacent to the gallbladder.

The presenting features of acute cholecystitis include fever, an elevated white cell count and persistent upper abdominal pain with signs of local peritonism overlying the gallbladder. Many patients admitted to hospital with biliary pain through the emergency department have biliary colic only and do not have acute cholecystitis. In practice, the vast majority are commenced on intravenous antibiotics, even though there may be no clinical evidence of acute infection. Patients with uncomplicated biliary colic require pain relief only and do not necessarily require hospital admission or

antibiotics unless their symptoms do not settle quickly.

Cholangitis

Stones that move from the gallbladder into the biliary tree or those that develop primarily in the intrahepatic or extrahepatic bile ducts (rare) can cause cholangitis (Figures 2a and b). The obstructing stone causes an increase in the intraductal pressure, leading to bile stasis and secondary multiorganism infection. Symptoms of cholangitis include right upper abdominal pain, jaundice and fever (known as Charcot's triad). Patients with cholangitis can become unwell quickly and usually require hospital admission for fluid resuscitation and broad-spectrum intravenous antibiotics. Cholangitis is an easy diagnosis to miss and should be considered in elderly patients who present with confusion and mildly abnormal liver function results.

Acute pancreatitis

Gallstones are one of the two most common causes of acute pancreatitis (the other is excessive alcohol). Acute pancreatitis results from a stone lodged in the distal common bile duct at the site where it meets the pancreatic duct. It is unclear whether the inflammatory process in the pancreas is initiated by a rise in the pancreatic ductal pressure or whether it is caused by reflux

of bile into the pancreatic duct. Regardless, the pain of pancreatitis is often severe and is mainly localised to the epigastrium, with direct radiation through to the back.

Patients with severe acute pancreatitis can deteriorate rapidly and usually require hospital admission for urgent fluid resuscitation and further investigation. If a stone is suspected or identified then early relief of the obstruction by endoscopic retrograde cholangiopancreatography (ERCP) is important.

Patients with small stones in the gallbladder and those with primary extrahepatic stones are most at risk of gallstone pancreatitis. Serum lipase level is the most sensitive test for diagnosing acute pancreatitis.

HOW SHOULD GALLSTONES BE INVESTIGATED?

A detailed clinical history is important to identify typical symptoms of gallstones. Often patients have already undergone other investigations (e.g. upper gastrointestinal endoscopy, cardiac investigations) before gallstones are diagnosed. In retrospect, many of the symptoms being investigated may be typically biliary, and an ultrasound examination would have revealed the diagnosis. In patients with truly atypical biliary pain, other less common gastrointestinal conditions, such as peptic ulcer disease or oesophagogastric



Figure 4. Laparoscopic view of an inflamed oedematous gallbladder (grade 2 inflammation).

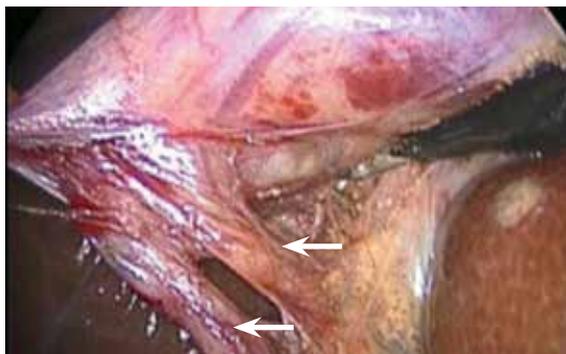


Figure 5. The 'critical view' of the biliary anatomy, as seen during a laparoscopic cholecystectomy, showing the gallbladder (top), cystic artery (upper arrow) and cystic duct (lower arrow).

malignancy, or nongastrointestinal problems such as cardiac disease should be ruled out.

A transabdominal ultrasound examination is simple and noninvasive, and has the highest sensitivity and specificity of any investigation for diagnosing gallstones (Figure 3). CT and MRI scans often fail to identify gallstones, even those that can be seen easily on ultrasound examination. The following features should be noted on ultrasound examination:

- presence or absence of stones within the gallbladder
- thickening of the gallbladder wall suggesting cholecystitis
- dilation of the extrahepatic ducts or the presence of a stone in the common bile duct.

Occasionally, CT or MR cholangiography may be required to exclude choledocholithiasis. These investigations are an excellent noninvasive means of examining the biliary tree. A CT cholangiogram should not be ordered if the serum bilirubin level is greater than 50 $\mu\text{mol/L}$ as higher levels can lead to poor opacification of the bile ducts.

ERCP may be necessary to remove common bile duct stones if there is a history of repeated episodes of cholangitis or pancreatitis. However, ERCP is usually reserved for patients with obstructive jaundice or a history of severe pancreatitis, or those who are unfit to undergo laparoscopic cholecystectomy. Some surgeons offer the option of exploration and removal of common bile duct stones at the time of laparoscopic cholecystectomy, potentially using laparoscopic choledochoscopy (Figure 2b).

Preoperative blood tests should include a liver function assessment and full blood count. Elevated liver function results, particularly elevated levels of the cholestatic enzymes alkaline phosphatase and gamma glutamyl transferase, suggest choledocholithiasis. A serum lipase level is the most sensitive and specific test for pancreatic inflammation and has largely replaced serum amylase level as a marker of acute pancreatitis.

Occasionally, patients present with typical biliary pain and yet no gallstones are seen on transabdominal ultrasound examination. In this situation, a cholescintigram

(HIDA scan) may be helpful to exclude delayed emptying of the gallbladder. Patients with typical biliary symptoms and a delayed ejection fraction, as demonstrated by a HIDA scan ($<35\%$ after stimulation with intravenous cholecystikinin), may benefit from laparoscopic cholecystectomy even if no stones are seen on ultrasound.⁴

TREATMENT OPTIONS

Cholecystectomy

Removal of the gallbladder is the most effective treatment for patients with symptomatic gallstones. Patients who are unfit for surgery and those who have symptoms related to choledocholithiasis (cholangitis, pancreatitis) should be offered an ERCP and sphincterotomy with removal of the extrahepatic bile duct stones. However, this intervention does not deal with the gallbladder, which is the source of the stones in most cases and usually the cause of the abdominal pain. Patients with true biliary colic or cholecystitis are likely to have ongoing symptoms after an ERCP alone. Repeated biliary colic or attacks of cholecystitis may be treated in the short term with pain relief and/or antibiotics, but only a cholecystectomy will resolve these symptoms definitively.

Patients often ask why the gallbladder has to be removed rather than just the gallstones. This is because removing the stones alone does not treat the underlying problem, which is an inability of the gallbladder to concentrate and empty in a normal fashion. Symptomatic patients have a nonfunctioning gallbladder, and a cholecystectomy improves quality of life because it removes the diseased organ causing the pain. In the months after surgery, the intrahepatic and extrahepatic bile ducts dilate slightly to compensate and deliver more bile from the liver as required.

How is a cholecystectomy performed?

Cholecystectomies are now performed laparoscopically, under general anaesthesia using three to four small abdominal incisions (Figure 4). In Australia, most patients remain in hospital overnight after surgery,

although some units perform this as a day procedure. In experienced hands, this operation is associated with minimal morbidity and almost negligible mortality risk.

Surgeons should provide detailed information to patients about the procedure and obtain informed consent. Specifically, they should explain the risks of bleeding, infection and injury to the extrahepatic bile duct. In experienced hands, the risk of bile duct injury is less than 1%.⁵ Appropriately trained surgeons routinely identify the main anatomical structures in order to avoid this injury (Figure 5). All referring doctors and their patients should enquire about a particular surgeon's record with laparoscopic cholecystectomy and whether they audit their surgical results.

Although open cholecystectomy is now rarely performed, it may occasionally be necessary because inflammation around the gallbladder makes laparoscopic dissection difficult. However, converting to an open procedure does not necessarily make the operation easier because of the anatomical magnification and clarity provided by the modern laparoscope. Patients who undergo open cholecystectomy usually remain in hospital for three to four days, compared with an overnight stay after laparoscopic cholecystectomy.⁶

Should every patient have an intraoperative cholangiogram during cholecystectomy?

There is ongoing debate about the need for routine cholangiography (x-ray of the main bile duct) during every laparoscopic cholecystectomy (Figure 2b). Those who advocate routine intraoperative cholangiography (IOC) argue that up to 10% of patients have unsuspected common bile duct stones. Furthermore, IOC allows accurate definition of the biliary anatomy and early recognition of bile duct injury if it occurs. Conversely, those who oppose routine IOC argue that it simply prolongs the procedure and that asymptomatic patients with common bile duct stones do not often have problems postoperatively. However, there are no long-term

data to support the latter assertion.

Long-term follow-up studies are urgently needed to resolve the issue of whether IOC should be routinely performed. Interestingly, most specialist hepatobiliary surgeons in Australia routinely perform IOC. In contrast, general surgeons tend to be more selective with IOC, with resulting greater use of pre- and post-operative ERCP.⁷

What can patients expect after their gallbladder is removed?

After cholecystectomy, there may be a slightly increased stool frequency for a few months. During this time, patients should avoid especially fatty food, but most return to their usual diet and have a normal quality of life soon after.

In the early postoperative period, some patients experience upper abdominal pain similar to their preoperative symptoms. This mostly settles quickly and does not require further intervention other than reassurance. However, patients who complain of severe or persistent pain in the immediate postoperative period should have an ultrasound examination to exclude a possible bleed or bile leak. A full blood count, liver function tests and serum lipase level should also be checked. It is important that patients have access to their hospital or surgical team during the early postoperative period if these symptoms occur.

If patients have undergone thorough history-taking and physical examination and have been found to have typical biliary symptoms and gallstones identified on ultrasound examination then a laparoscopic cholecystectomy will relieve symptoms in approximately 95% of cases. A small proportion (ideally fewer than 5%) may have ongoing symptoms, suggesting either residual stones in the extrahepatic bile duct, biliary dyskinesia or an unrecognised nonbiliary diagnosis.

The term 'postcholecystectomy syndrome' is used to describe patients who have ongoing abdominal symptoms after a cholecystectomy. Most patients labelled with this diagnosis have either biliary

dyskinesia or a nonbiliary cause for their pain. Unfortunately, this pejorative term has led to the widespread myth that patients often develop worse symptoms after their gallbladder is removed. This is incorrect, and many of these patients have a missed diagnosis, such as peptic ulcer disease, irritable bowel syndrome, hepatic flexure syndrome (adhesions to the ascending colon and hepatic flexure) or even renal tract pathology.

In a minority of patients, a cholecystectomy may unmask an underlying upper gastrointestinal motility disorder that principally affects the biliary tract (e.g. they may have been diagnosed with irritable bowel syndrome). These patients have true biliary dyskinesia, a specific motility disorder that may require further investigation with biliary manometry (pressure readings of the sphincter of Oddi). Occasionally, an ERCP and sphincterotomy may be necessary to relieve the extrahepatic biliary tree pressure in patients with persistent symptoms.

Nonsurgical treatments

As discussed above, cholecystectomy is the only definitive way to remove the cause of recurrent biliary pain or acute cholecystitis. ERCP and sphincterotomy with removal of common bile duct stones may temporarily resolve the complications of cholangitis or pancreatitis but on their own will not prevent further biliary colic or infection of the gallbladder.

In the short term, repeated biliary colic or attacks of cholecystitis may be treated with pain relief and/or antibiotics. These should be offered in conjunction with a strict low-fat diet to patients who are unfit for surgery (e.g. elderly patients and those with cardiac or respiratory disease that precludes general anaesthesia). Although this treatment may reduce the number and severity of attacks there is no certainty it will resolve the symptoms.

Other nonsurgical options for patients with symptomatic gallstones who cannot undergo laparoscopic cholecystectomy include the following.

Pharmacological oral dissolution therapy.

Bile acids such as chenodeoxycholic acid and ursodeoxycholic acid can dissolve some cholesterol stones. These drugs are given orally but need to be taken for many months (and sometimes several years) and are effective only for noncalcified stones less than 5 mm in diameter. As these drugs are not available on the PBS they are costly for patients, and ultimately they do not deal with the underlying gallbladder abnormality.

Contact dissolution. This involves directly instilling a drug, methyl tert-butylether, into the gallbladder with the aim of dissolving small cholesterol stones. However, this may cause severe irritation of the gallbladder, leading to potential complications such as infection and perforation.

Mechanical disruption. Techniques such as extracorporeal shock-wave lithotripsy or laser ablation are used regularly to treat renal tract stones, but are relatively invasive treatments for gallstones and may injure adjacent liver or bile ducts. Also, the production of small stone fragments that can pass into the main bile duct may increase the risk of pancreatitis. For these reasons, mechanical disruption is not used routinely to treat gallstones.

Percutaneous cholecystostomy. This involves drainage of the gallbladder through insertion of a catheter under radiological guidance. This is a temporising procedure that may be helpful for extremely ill patients with acalculous cholecystitis who are unfit for laparoscopic cholecystectomy. It may also be used in some patients with calculous cholecystitis sepsis who are unfit for general anaesthesia. However, the presence of stones within the gallbladder complicates the situation when the drain is eventually removed. Commonly, these patients continue to have symptoms that require cholecystectomy.

ASYMPTOMATIC GALLSTONES

About 17% of patients with gallstones have no symptoms and have not felt a need to modify their diet ('silent' gallstones).^{8,9} For patients with incidentally discovered asymptomatic gallstones, a conservative

approach is usually recommended. This is based on long-term observational studies showing an overall low risk of developing symptoms or complications, which has to be weighed against the risks and morbidity of a cholecystectomy.

Several population-based cohort studies have shown that the risk of symptoms developing in patients with incidentally discovered gallstones, although low, are not insubstantial. Symptoms develop in around 2 to 4% of patients annually and this risk is cumulative for the rest of the patient's life.⁸⁻¹⁰ Overall, the course is benign for most patients, and it is not clear why some go on to develop symptoms or complications. Patients should be questioned specifically about subtle abdominal symptoms or food intolerance that may be longstanding and may have been dismissed as their 'normal digestion'. Once severe gallstone symptoms develop problems may be ongoing and attacks of pain are frequently unpredictable. The interval between attacks may vary from several days to many years.

In this era of minimally invasive surgery, the risk of developing symptoms and complications should be weighed against the similarly small risks of laparoscopic cholecystectomy in appropriately trained hands and the low risk of general anaesthesia in otherwise healthy patients. Many clinicians believe it is reasonable to consider laparoscopic cholecystectomy for selected patients with incidentally discovered asymptomatic gallstones. This is provided they have a low risk for general anaesthesia and are fully informed of the rationale for this approach.

Some patients with asymptomatic gallstones are not happy to accept even a small chance of developing symptoms. Patients who are planning to travel may be concerned about developing symptoms when away from home and many raise the issue of whether they should declare asymptomatic gallstones when applying for travel insurance. There are no clear guidelines and each case should be considered individually. Furthermore, some patients have conditions such as diabetes or immunosuppression that increase their risk of

infectious complications if symptoms develop. Occasionally patients such as these are referred for cholecystectomy as a prophylactic intervention.

It is impossible to give sound advice to patients with asymptomatic incidentally discovered gallstones other than to inform them about potential symptoms, what is involved in a laparoscopic cholecystectomy and its low risks. In the end, patients need to make the final decision.

CONCLUSION

Gallstones are common in Western societies. A history of epigastric or right-sided abdominal pain, nausea or abdominal bloating, especially after meals, is a red flag for gallstone disease. Transabdominal ultrasonography is the investigation of choice for possible gallstones as it is non-invasive, relatively cheap and has higher sensitivity than CT and MRI. For patients with symptomatic gallstones, laparoscopic cholecystectomy is the treatment of choice, leading to symptom resolution in more than 90% of patients. MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS: None.

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