

# CLINICAL REVIEW

## Gallstones

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Gallstones affect approximately 5-25% of adults in the Western world. It is therefore important to understand the consequences of a diagnosis of gallstones, the associated complications, and treatment to allow patients to be appropriately advised. The purpose of this review is to update clinicians on the diagnosis and management of gallstones.

### What are gallstones?

Gallstones are crystalline deposits in the gallbladder (figure 1).<sup>1</sup> The prevalence of gallstones varies between 5% and 25%, with a higher prevalence in Western countries, women, and older age group.<sup>2</sup> Traditionally, gallstones were classified as cholesterol stones, pigment stones, or mixed stones (a combination of cholesterol and pigment stones) based on their composition,<sup>3</sup> which can only be determined reliably after their removal.<sup>4</sup> Recently, additional types of gallstones have been identified based on their microscopic structure and composition.<sup>1</sup> However, most stones fall under the umbrella of cholesterol (37-86%), pigment (2-27%), calcium (1-17%), or mixed (4-16%).<sup>1-4</sup> The types of gallstone vary by their cause, the measures attempted to prevent their formation, their appearance on radiographs, and their response to dissolution therapy. The current recommendations for diagnosis and management are, however, the same for all types of gallstone.

### Who gets gallstones?

Cholesterol stones are formed because of the alteration in the balance between pronucleating factors and antinucleating factors in the bile. Factors that lead to gallstone formation include excessive bile cholesterol, low bile salt levels, decreased gallbladder motility, and the phosphatidylcholine molecule, which prevents the crystallisation of cholesterol.<sup>5</sup> The main risk factors for cholesterol stone formation include female sex, pregnancy, high dose oestrogen treatment, increasing age, ethnicity (higher prevalence in Native American Indians and lower prevalence in black Americans, Africans, and people from China, Japan, India, and Thailand), genetic traits, obesity, high serum triglyceride levels, low levels of high density cholesterol, rapid weight loss, high calorific diet, refined carbohydrate diet, lack of physical activity, cirrhosis, Crohn's disease, and gallbladder stasis (for example, as a result of previous

gastrectomy or vagotomy).<sup>6-8</sup> Haemolysis and chronic bacterial or parasitic infections are considered the main risk factors for pigment stones<sup>5</sup> and are preventable causes of gallstones.

### Can gallstone formation be prevented?

Although some of the causes of gallstones, such as obesity, rapid weight loss, a high calorific diet, a refined carbohydrate diet, and lack of physical activity are preventable by lifestyle changes, there is currently no evidence that lifestyle modifications can reduce the incidence of gallstones. Haemolysis and infections can be prevented by early recognition of sickle cell disease, taking appropriate measures for prevention of sickling crises, and using prophylactic antibiotics in those who have undergone splenectomy or had splenic infarction. Another way of preventing gallstone formation is to remove the gallbladder in people undergoing anti-obesity operations (as rapid weight loss is one of the risk factors for gallstone formation) and other major abdominal operations to avoid further surgery as a result of the development of symptomatic gallstones. There is currently no evidence to suggest that prophylactic cholecystectomy is indicated in any patient group without gallstones<sup>9</sup> or that any of the above suggested measures of preventing gallstones are effective.

### How do gallstones present?

Each year approximately 2-4% of people with gallstones develop symptoms, with biliary colic being the most common symptom (steady right upper quadrant abdominal pain lasting more than half an hour)<sup>10-14</sup> in the absence of fever. Presence of fever usually indicates acute cholecystitis or cholangitis. Other common symptoms related to gallstones include epigastric pain and intolerance to fried or fatty foods (symptoms such as nausea, bloating, flatulence, frothy and foul smelling stools).<sup>14</sup> The box lists the complications resulting from gallstones, and includes acute cholecystitis (0.3-0.4% annually),<sup>11-13 15</sup> acute pancreatitis (0.04-1.5% annually),<sup>15</sup> obstructive jaundice (0.1-0.4% annually),<sup>12 13 15</sup> and other rarer complications such as acute cholangitis and intestinal obstruction (gallstone ileus). Of these, acute pancreatitis and cholangitis are life threatening complications, with 3% to 20% mortality after a first attack of acute pancreatitis<sup>16</sup> and 24% mortality after acute cholangitis.<sup>17</sup>

**Summary points**

- Gallstones are common in adults
- Currently, treatment is indicated only for symptomatic gallstones
- Pain is the most common symptom related to gallstones
- Occasionally gallstones present with life threatening complications
- Surgery is the only definitive treatment and is recommended for people with symptomatic gallstones who are fit to undergo surgery
- Laparoscopic cholecystectomy is currently the preferred method of surgery and is generally both effective and safe; however, there is a 0.3% risk of serious injury to the bile duct, which may have serious long term consequences

**Sources and selection criteria**

We searched Medline, Embase, the Cochrane Database of Systematic Reviews, and Clinical Evidence online using the search terms "gallstones" or "cholelithiasis", focusing mainly on systematic reviews, meta-analyses, and high quality randomised controlled trials published within the past five years, wherever appropriate and possible.

Uncomplicated biliary colic often precedes other gallstone related complications.<sup>11</sup> The rates of gallstone related complications are higher in people with a history of uncomplicated biliary colic.<sup>18</sup> Although studies have shown an association between gallstones and cancer of the biliary tract,<sup>19 20</sup> no causative link has been established and the observed association could be due to the presence of common factors causing gallstones and gallbladder cancer.<sup>21</sup>

**How should suspected gallstones be investigated?**

Ultrasonography is currently the first line method for the diagnosis of gallstones and has a high diagnostic accuracy (90% sensitivity and 88% specificity) even when performed by non-radiologists.<sup>22</sup> Based on the agreement in a consensus conference, the diagnosis of acute cholecystitis is suspected by the presence of local or systemic signs of inflammation, such as Murphy's sign (tenderness in the right upper quadrant below the costal margin on deep inspiration; sensitivity 65% and specificity 87%<sup>23</sup>), fever, increased white cell count or C reactive protein, and confirmed by ultrasonography, computed tomography, or magnetic resonance imaging.<sup>24</sup> Radiological signs of acute cholecystitis include a thickened gallbladder wall (>4 mm), an enlarged gallbladder (long axis diameter >8 cm, short axis diameter >4 cm), or fluid collection around the gallbladder.<sup>24</sup> The diagnosis of pancreatitis is usually suspected by the presence of pain in the epigastric region radiating to the back and confirmed by diffuse abdominal tenderness, increased serum amylase, urine amylase, or serum lipase levels, and is supported by radiological features such as an enlarged pancreas with peripancreatic fluid collections.<sup>25</sup> The consensus conference conducted by the European Association for Endoscopic Surgery concluded that common bile duct stones should be suspected by the presence of clinical features suggestive of obstructive jaundice, such as yellowish discoloration of skin and dark urine supported by an increased serum bilirubin or alkaline phosphatase level and confirmed with magnetic resonance cholangiopancreatography or endoscopic ultrasonography.<sup>26 27</sup> Fever and rigors in the presence of jaundice should raise the suspicion of cholangitis.

If patients present with symptoms suggestive of gallstones, are systemically well, and do not have features suggestive of acute cholecystitis, acute pancreatitis, obstructive jaundice, or cholangitis, it is reasonable to investigate them by an elective ultrasonography, followed by elective referral to a general surgeon if gallstones are present. If gallstone complications are suspected, urgent referral to the surgeon is warranted because

early confirmation of diagnosis and treatment of complications are associated with better outcomes (see section on timing of surgery). Features that suggest the presence of complications include fever, rigors, hypotension, epigastric pain radiating to the back, dark urine, jaundice, Murphy's sign, diffuse abdominal tenderness, or a positive result for urine bile pigments on urinalysis. Depending on the clinical presentation, further blood tests, such as blood white cell count, levels of serum C reactive protein, serum amylase, serum bilirubin, and serum alkaline phosphatase; urine tests to check levels of urine amylase and urine lipase; and radiological investigations such as ultrasonography, computed tomography, magnetic resonance imaging, magnetic resonance cholangiopancreatography, and endoscopic ultrasonography may be performed to confirm or rule out the presence of gallstones and complications.

**How is gallstone disease treated?****Asymptomatic gallstones**

The distinction between symptomatic and asymptomatic gallstones can be difficult as symptoms can be mild and varied. While gallstone complications can be diagnosed using one or more of the criteria described, in patients presenting with vague upper abdominal pain or dyspeptic symptoms it can be difficult to discern whether the symptoms are related to gallstones. In one study, 90% of patients with classic biliary colic had high rates of symptom relief after cholecystectomy, suggesting that biliary colic is a fairly reliable indicator of symptomatic gallstones.<sup>28</sup> Around 70% of patients with upper abdominal pain with no further restriction by intensity or duration of pain had symptom relief after cholecystectomy. Only 55% of patients with dyspeptic symptoms had symptom relief, suggesting that in a major proportion of people vague upper abdominal pain or dyspepsia may not be related to gallstones.<sup>28</sup> There is currently no evidence that lifestyle modifications such as decreasing fatty food intake or increasing exercise decreases or prevents the incidence of symptoms in people with asymptomatic gallstones. No treatment is currently recommended for patients with asymptomatic gallstones (irrespective of whether these are cholesterol, pigment, or mixed stones) except for patients with porcelain gallbladders (which is usually identified by ultrasonography), owing to the association with gallbladder cancer.<sup>29</sup> The reason for advising against surgery for asymptomatic gallstones is because of the complications associated with surgical intervention, although this is a topic of ongoing debate.

In patients with asymptomatic gallstones undergoing major abdominal surgery, it seems reasonable to offer

### Complications of gallstones

- Acute cholecystitis
- Choledocholithiasis
- Acute cholangitis
- Acute pancreatitis
- Mucocele of gallbladder
- Empyema of gallbladder
- Gangrenous gallbladder
- Biliary peritonitis
- Porcelain gallbladder
- Gallbladder cancer

cholecystectomy, as adhesions related to a major operation may make further minimal access surgeries difficult or impossible. There is, however, no evidence from randomised controlled trials or systematic reviews to support this statement.

### Symptomatic gallstones

Cholecystectomy (removal of the gallbladder) is the preferred option in the treatment of gallstones, irrespective of whether the gallstones are cholesterol, pigment, or mixed stones. Evidence from randomised controlled trials, systematic reviews, and cohort studies show that extracorporeal shock wave lithotripsy or bile acid dissolution therapy with ursodeoxycholic acid has a low rate of cure, with only 27% of patients having dissolution of stones after treatment with ursodeoxycholic acid and only 55% of carefully selected patients being stone free after extracorporeal shock wave lithotripsy. The rate of recurrent gallstones is also high; more than 40% of patients have recurrence of gallstones within four years after complete dissolution of stones or extracorporeal shock wave lithotripsy. Over three months, only 26% of people remained colic free after treatment with ursodeoxycholic acid compared with 33% after placebo, and about 2% of people had gallstone complications after treatment with ursodeoxycholic acid, which is similar to the annual rate of complications in those not taking the drug.<sup>15 30-34</sup> In patients who are not suitable for cholecystectomy because of their general medical condition, percutaneous cholecystostomy (temporary external drainage of the gallbladder contents through a tube inserted under radiological guidance) may be considered in an emergency situation, although a systematic review revealed that the role of percutaneous cholecystostomy in the management of such patients was not clear.<sup>35</sup> When the patient's condition has improved, cholecystectomy may be reconsidered. Based on evidence from randomised controlled trials, watchful observation may be a suitable alternative to surgery in a small proportion of people who do not get recurrent symptoms.<sup>36 37</sup> It is, however, not possible to predict those patients who will get recurrence of symptoms.

### *Cholecystectomy: the risks and benefits*

Although cholecystectomy is a relatively safe procedure with few serious complications, bile duct injury resulting from surgery is a serious complication, with potential long term consequences.<sup>38</sup> The overall short term mortality after surgery varies between 0% and 0.3%.<sup>9</sup> Although traditionally less than 0.5% of people undergoing cholecystectomy are believed to have bile duct injury,<sup>9</sup> a study of more than 50 000 unselected patients from the Swedish Registry for Gallstone Surgery and ERCP, GallRiks, revealed that 1.5% of patients undergoing cholecystectomy between 2005 and 2010 developed a bile duct injury, although only a fifth of these injuries (0.3%) involved

partial or complete transection of the bile duct.<sup>38</sup> The patients with bile duct injury had a significantly higher one year mortality compared with those without such an injury.<sup>38</sup>

Cholecystectomy is generally performed by key hole operation (laparoscopic cholecystectomy)<sup>39</sup> because of the shorter length of hospital stay, decreased pain, earlier return to work, and better cosmesis. Laparoscopic cholecystectomy can be performed as a day procedure and generally involves four incisions measuring less than 1 cm each. Fat intolerance may develop in a small proportion of people after cholecystectomy, and a low fat diet is recommended in these patients. However, there is currently no strong evidence to support the usefulness of such a diet.

In patients with symptomatic gallbladder stones and common bile duct stones, the treatment options include open cholecystectomy with open exploration of the common bile duct, laparoscopic cholecystectomy with laparoscopic exploration of the common bile duct, and laparoscopic cholecystectomy with endoscopic sphincterotomy (performed preoperatively, intraoperatively, or postoperatively).<sup>40</sup> Evidence from a systematic review of randomised controlled trials shows that there is no evidence of difference in the morbidity or incidence of retained stones between endoscopic sphincterotomy and laparoscopic exploration of the common bile duct and inconsistency as to whether there is any difference in the length of hospital stay between the two approaches.<sup>40</sup>

### *When is the optimum time for surgery?*

The timing of surgery for various indications is controversial. In patients with biliary colic there is no medical reason to delay surgery, the delays being caused only by the availability of resources (although surgery can be delayed by surgeons recommending weight reduction for particular patients). Evidence from a randomised controlled trial, which compared early surgery within 24 hours of hospital admission versus delayed surgery with an average wait of about four months on the waiting list, showed that delaying surgery increased complications (0% in early group versus 22.5% in the delayed group) and hospital stay (an average of one additional day).<sup>41</sup> The timing of cholecystectomy in patients with acute cholecystitis is also controversial. Although the traditional belief was to allow the inflammation to settle and perform laparoscopic cholecystectomy after a period of at least six weeks, a systematic review on this topic has shown that early laparoscopic cholecystectomy performed within one week of onset of symptoms can avoid further complications from gallstones while waiting for surgery.<sup>42</sup> Early laparoscopic cholecystectomy can also decrease hospital stay by about four days without increasing surgical complications (approximately 5-6% in each group) or the proportion of people requiring conversion from laparoscopic to open surgery (approximately 20% in each group).<sup>42</sup> Although

most of the gallbladder related complications during the waiting time in the delayed group in the studies included in the systematic review were recurrence or non-resolution of acute cholecystitis, there is potential for further episodes of pain, pancreatitis, or obstructive jaundice while waiting. Evidence from a randomised controlled trial showed that morbidity after laparoscopic cholecystectomy between seven and 45 days was approximately two or three times that of surgery performed early; hence surgery within this timeframe is not recommended.<sup>43</sup> For timing of surgery in patients with mild acute pancreatitis (no organ failure or local complications), evidence from a systematic review that included only one small randomised controlled trial showed that performing surgery as early as possible (rather than waiting until symptoms settle and for blood test results to return to normal levels) decreased the hospital stay by one day,<sup>44</sup> although experts have expressed concerns that the severity of pancreatitis may not be evident until 48 hours and surgery in patients with severe pancreatitis (organ failure or local complications) within 48 hours can be harmful.<sup>45</sup> Delaying surgery for 48 hours overcomes this concern. The two circumstances where early cholecystectomy may not be appropriate are in patients with severe acute pancreatitis and those presenting during pregnancy.<sup>9,44</sup> Further trials are necessary to resolve these problems.

## What is the impact of gallstone disease on health services and society?

In 2004 in the United States, a total of 1.8 million outpatient visits were related to gallstones.<sup>46</sup> Each year, more than 0.5 million cholecystectomies are performed in the United States<sup>47</sup> and 70 000 in England.<sup>48</sup> The cost of cholecystectomy and loss of working time because of symptoms related to gallstones, and their treatment has an important impact on health services and society.

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**Questions for future research**

Can lifestyle modifications such as increased physical activity, a low fat diet, and avoidance of high calorific and refined sugar diet prevent or reduce the development of gallstones or can they decrease the incidence and severity of symptoms related to gallstones?

What is the optimal timing of cholecystectomy in patients with acute severe pancreatitis and pregnant women with symptomatic gallstones?

What is the optimal surgical technique to avoid complications related to laparoscopic cholecystectomy?

What is the optimal approach to reducing the symptoms of cholecystectomy and facilitating increased day case surgery and earlier return to work?

What new approaches could be used in patients with symptomatic gallstones who are unfit to undergo surgery?

**Tips for non-specialists**

If biliary colic is suspected, ultrasonography remains the first line investigation to establish whether gallstones are present

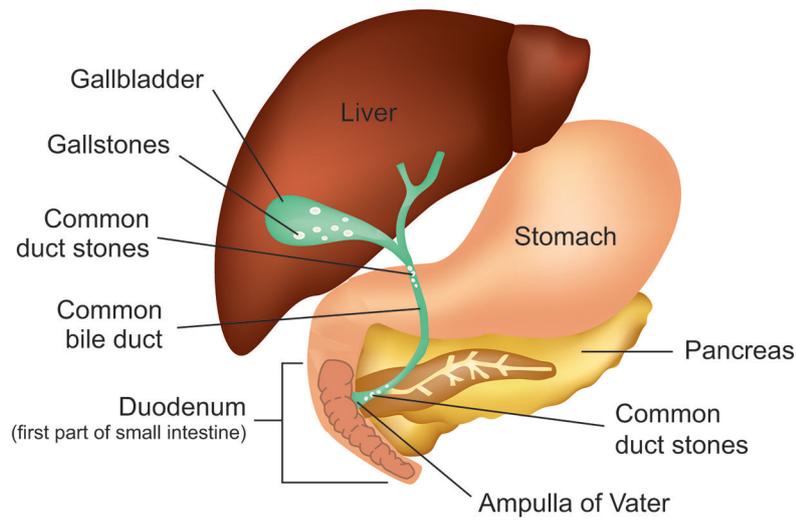
If acute cholecystitis or acute gallstone pancreatitis is suspected, emergency investigations and immediate referral to a specialist are recommended, as early surgery may be indicated

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## Figure



Obstruction to the common bile duct by common duct stones may cause jaundice or cholangitis. Obstruction to the pancreatic duct or ampulla of Vater by common duct stones may cause pancreatitis