

Tailor treatment to the patient with gallstone disease

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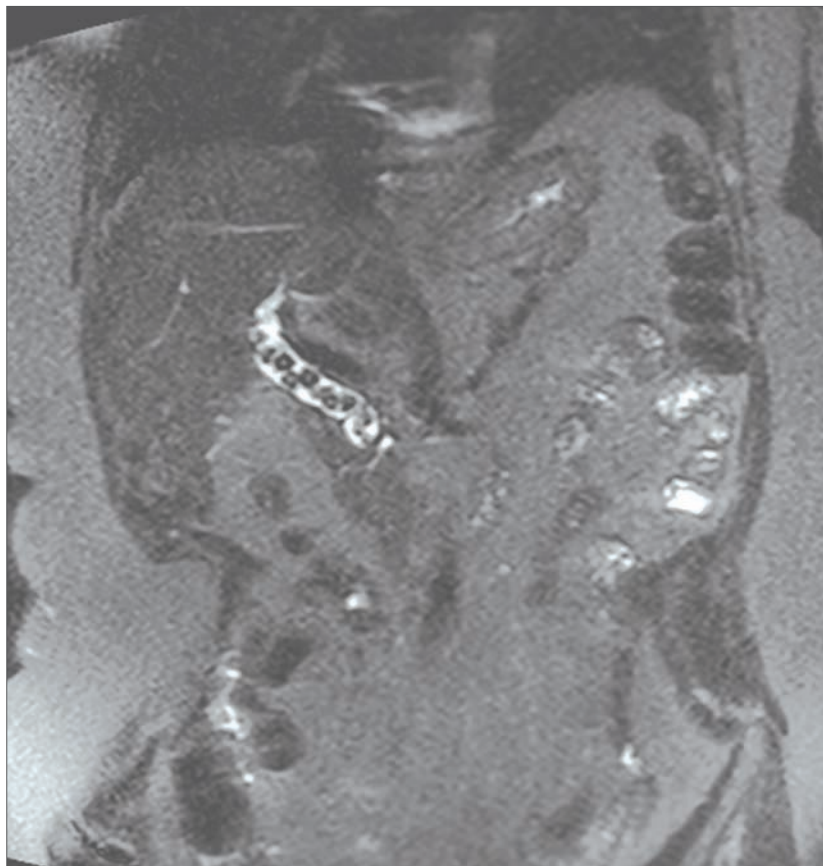


FIGURE 1

MRCP image indicating multiple stones (black opacifications) within the common bile duct



GALLSTONE DISEASE AFFECTS UP TO 15% OF PATIENTS IN THE UK.¹ IT IS ONE OF THE MOST

common reasons for gastroenterology admissions in Europe.² In the Western world, most gallstones are cholesterol stones (90-95%).³ The remainder are either pigment, calcium or mixed stones.⁴

Around 50-70% of patients with gallstones are asymptomatic at the time of diagnosis, the gallstones are detected incidentally, and most have a benign course. Overall, 10-25% of patients will go on to develop symptomatic gallstone disease.^{5,6}

The most common symptom of gallstones is abdominal pain, historically thought of as 'biliary colic', although a recent study found the pain was equally likely to be epigastric (43%) or in the right upper quadrant (41%).⁷ This is a steady pain that is non-paroxysmal in

nature lasting for more than 30 minutes but less than 8 hours, and classically is maximal within 30 minutes.

It is frequently triggered by fatty foods and is experienced as a severe pain that may be associated with nausea and vomiting but not fever or abdominal tenderness. The pain can radiate to the

Table 1

Differential diagnoses of gallstone disease³²

- Acute hepatitis
- Bile duct stricture
- Gallbladder polyps
- Gastro-oesophageal reflux disease
- Irritable bowel syndrome
- Non-biliary acute pancreatitis
- Peptic ulcer disease
- Tumours of the gallbladder, liver, stomach, gut and pancreas

Which patients are at increased risk?

What are the potential complications?

What are the treatment options?

interscapular region or right shoulder.

A proportion of patients will present with atypical symptoms such as dyspepsia. As asymptomatic gallstones and dyspepsia are common in the general population they frequently coexist but patients who undergo cholecystectomy for dyspepsia attributed to gallstones do not have a good clinical outcome and symptoms may persist in up to 20% of cases post cholecystectomy.⁸

A recent systematic review and meta-analysis found that the majority (65.7%) of patients with symptomatic uncomplicated gallstones had symptoms similar to functional dyspepsia, either in association with biliary colic or as the predominant symptom. Between 37 and 40% of patients had persistent abdominal symptoms following cholecystectomy. The authors concluded that 'cholecystectomy for dyspeptic

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symptoms alone is unjustified.⁹

If patients present with atypical symptoms an alternative underlying cause may be present and should be investigated accordingly. Differential diagnoses for gallstone disease are listed in table 1, p15. Patients may also present with complications of gallstone disease, see table 2, below. These include cholecystitis, obstructive jaundice, cholangitis and gallstone pancreatitis.

CAUSES AND RISK FACTORS

Cholesterol and pigment gallstones originate from an interaction of genetic, environmental and metabolic abnormalities. In Western populations brown pigment stones are found in the bile duct post cholecystectomy and in primary sclerosing cholangitis but in

South East Asian populations they occur with chronic infection.⁵

Most stones are cholesterol stones and several factors increase the risk of cholesterol stone formation. Obesity is associated with an increased risk of symptomatic gallstones necessitating cholecystectomy.

Other factors associated with metabolic syndrome including insulin resistance, dyslipidaemia (low HDL and hypertriglyceridaemia), sedentary lifestyle and fast food consumption are also associated with the formation of cholesterol gallstones.⁶ Insulin resistance and type 2 diabetes are strongly associated independent of obesity. The European Association for the Study of the Liver (EASL) guideline recommends that 'healthy lifestyle and food, regular

physical activity and maintenance of an ideal body weight might prevent cholesterol gallbladder stones and symptomatic gallstones.¹³

Patients should be advised to reduce their consumption of refined carbohydrates and saturated fats, and increase their fibre intake.

Rapid weight loss (> 1.5 kg/week) is also a risk factor for cholesterol stone formation¹⁰ whereas moderate weight loss (< 1.5 kg/week) is protective against new gallstone formation.⁷ Bariatric surgery is also a risk factor, which may have implications should those patients go on to develop common bile duct stones and conventional access for endoscopic therapy with an endoscopic retrograde cholangiopancreatography (ERCP) is not possible, for example

Table 2

Common gallstone complications and their management

	Biliary colic	Cholecystitis	Choledocholithiasis	Cholangitis	Pancreatitis
Mechanism	Intermittent obstruction of cystic duct or bile ducts No inflammation or infection	● Acute gallbladder inflammation due to impacted stone in cystic duct ● About 50% have secondary bacterial infection	● Stone passed from gallbladder into bile duct or formed in the bile duct	● Bile duct stone causing bile stasis and infection	● Pancreatic duct obstruction due to gallstones
Symptoms	Intermittent epigastric or right upper quadrant (RUQ) pain lasting < 8 hours	● Consistent epigastric/RUQ pain lasting > 6 hours. ● Often history of past biliary pain ● Nausea and vomiting	● Often asymptomatic ● Otherwise indistinguishable from biliary pain	● RUQ or epigastric pain ● Jaundice ● Fever ● Delirium ● Shock	● Severe epigastric abdominal pain
Clinical findings	Mild epigastric and/or RUQ tenderness	● Murphy's sign ● Fever	● Often normal ● Otherwise indistinguishable from biliary pain	● Fever ● RUQ pain ● Jaundice	● Severe epigastric pain ● Often peritonitic
Blood results	Normal liver function tests (LFTs). If abnormal suggests choledocholithiasis	● Mildly abnormal LFTs even in the absence of a stone ● Raised inflammatory markers ● Significant elevation of ALP/GGT suggests choledocholithiasis	● Abnormal LFTs – usually raised bilirubin/ALP ● ALT 'spike' indicates likely passage of a stone	● Raised inflammatory markers ● Abnormal LFTs – predominantly 'obstructive' (raised ALP/GGT and bilirubin) ● Positive blood cultures	● Raised inflammatory markers ● Abnormal LFTs ● Significant ALT rise indicates likely passage of a stone
Imaging	Abdominal ultrasound (US)	● Abdominal US ● Abdominal computerised tomography (CT)	● Abdominal US ● MRCP ● EUS	● Abdominal US ● MRCP	● Abdominal CT ● MRCP
Treatment	Cholecystectomy	● Antibiotics ● Cholecystectomy ● EUS placed gallbladder LAMS if severe and not a surgical candidate ● Percutaneous transhepatic gallbladder drainage (PTD)	● ERCP or bile duct exploration ● Cholecystectomy	● Antibiotics ● ERCP ● PTD ● Cholecystectomy	● IV fluids ● Nutrition ● ERCP if biliary obstruction or cholangitis ● Treat complications of pancreatitis

EUS = endoscopic ultrasound MRCP = magnetic resonance cholangiopancreatography ERCP = endoscopic retrograde cholangiopancreatography LAMS = lumen apposing metal stents

following Roux-en-Y gastric bypass.

Other risk factors for cholesterol stones include female gender, pregnancy, hormone replacement therapy (HRT) and advancing age. The risk is substantially lower with transdermal compared with oral HRT.¹¹ There is a lower incidence in black Americans, and those of African, Chinese, Indian, Japanese and Thai ethnicity. Crohn's disease and cirrhosis are also risk factors for cholesterol stone formation.⁴ Low alcohol intake and high coffee consumption are associated with gallstone formation in males.¹²

Haemolysis and chronic bacterial or parasitic infections are the main risk factors for pigment stones and are preventable causes of gallstones.¹³

DIAGNOSIS

Investigations are needed primarily to confirm the diagnosis of gallstones and also to identify patients with gallstones within the bile duct. It is imperative that a laparoscopic cholecystectomy should only be carried out when the bile duct is clear of stones (otherwise a post-cholecystectomy bile leak via the cystic duct stump is more likely).

Patients with symptoms suggestive of gallstones should be offered liver function tests and an abdominal ultrasound in line with NICE guidance on gallstone disease and British Society of Gastroenterology (BSG) guidance on common bile duct stones.^{14,15} Patients with confirmed gallstones on ultrasound presenting with typical symptoms should be referred to secondary care for surgical assessment and consideration of cholecystectomy.

A Cochrane systematic review on the performance of ultrasound and liver function tests (LFTs) for the diagnosis of common bile duct stones noted that the sensitivity for ultrasound varies widely but the summary sensitivity was 0.73 and the specificity 0.91.¹⁶ Therefore, patients in whom gallstones are strongly suspected despite normal ultrasound findings warrant further investigation.

To determine if patients have common bile duct stones, NICE recommends magnetic resonance cholangiopancreatography (MRCP), see figure 1, p15, for those who have abnormal LFTs and/or an ultrasound scan demonstrating dilated ducts as either of these features might indicate a common bile duct stone.¹⁵

A Cochrane systematic review of MRCP reported a sensitivity of 0.93 and specificity of 0.96 for identifying common bile duct stones.¹⁷ Endoscopic ultrasound is equivalent to MRCP at

identifying common bile duct stones.¹⁸ MRCP has the advantages of being more widely available, minimally invasive and enables imaging of the intrahepatic ducts.

Endoscopic ultrasound is less widely available but may be preferential or necessary in patients who are claustrophobic, have cardiac or metal implants or who are morbidly obese.¹⁴ Endoscopic ultrasound may also be advantageous if there is a high index of suspicion of a common bile duct stone as the patient can proceed immediately to an ERCP to clear the bile duct at the same time.

COMPLICATIONS

Complications of gallstones can range from pain alone to life-threatening sepsis and end organ damage. Patients with asymptomatic gallbladder stones need no intervention as most remain asymptomatic throughout life.

Biliary pain

Biliary pain can arise from gallbladder, cystic duct and bile duct stones (choledocholithiasis). This is the most common presentation of gallstone disease accounting for up to 75% of symptomatic gallstone presentations.¹

Cholecystitis

Cholecystitis is the most common complication of gallstones. It occurs in about 10% of patients with symptomatic gallstones¹⁹ and is the underlying cause in 3–9% of patients presenting to accident and emergency with acute abdominal pain.³ The most common cause of cholecystitis is a gallstone blocking the cystic duct.

The presentation of cholecystitis is similar to that of biliary pain. Typically, it lasts longer (more than 6 hours) and has accompanying signs of fever and raised inflammatory markers. Examination may reveal a positive Murphy's sign; halted inspiration during deep inspiration on palpation of the right upper quadrant. This occurs as a result of the inflamed gallbladder coming into contact with the examiner's hand causing significant discomfort.

Choledocholithiasis

The presentation of choledocholithiasis is indistinguishable from gallbladder stones. However, it is vital that patients with choledocholithiasis are identified before referral for cholecystectomy as bile duct clearance should occur prior to surgery. For patients with incidental, asymptomatic choledocholithiasis bile duct clearance is also recommended, as

without intervention up to 25% will develop complications.³

Cholangitis

Patients with choledocholithiasis can also present with infection of the biliary tree (cholangitis). Raised intraductal pressure secondary to obstruction causes the spaces between the cells lining the duct to widen resulting in contaminated bile coming into contact with the bloodstream.²⁰ This can result in life-threatening bacteraemia and biliary sepsis. Patients typically present with pain often in the presence of fever and jaundice (Charcot's triad). The sensitivity of Charcot's triad is very low (around 26%). Pain can be absent, especially in elderly patients, and only two-thirds of patients are jaundiced. The Tokyo diagnostic criteria specify fever or lab evidence of an inflammatory response plus jaundice or abnormal LFTs plus imaging evidence of biliary obstruction.²¹ Delirium and septic shock may also be present (Reynold's pentad) and indicate a more severe clinical presentation.

Pancreatitis

Around 50% of acute pancreatitis episodes in the UK are due to gallstone disease.²² History and examination may be indicative of acute pancreatitis and two out of the following three criteria need to be met for diagnosis:

- Typical history
- Elevated serum amylase or lipase (> 3 times the upper limit of normal)
- Imaging (CT, MRI or ultrasound) consistent with acute pancreatitis.²³

An ALT > 150 IU/L has a 95% positive predictive value for identifying gallstones as the causative insult.²⁴

MANAGEMENT

Management of gallstone complications depends on the presentation although the principles of treatment are the same in all cases; to ensure that the bile ducts are clear followed by cholecystectomy.

Patients with proven gallstones and uncomplicated biliary pain should be referred for routine laparoscopic cholecystectomy. Several meta-analyses have demonstrated that early cholecystectomy for patients with acute cholecystitis has comparable outcomes but shortens length of hospital stay.^{25,26} The EASL recommends cholecystectomy within 72 hours in cases of cholecystitis.³

While the natural history of bile duct stones is not fully understood the evidence suggests patients with choledocholithiasis should have stone clearance prior to cholecystectomy if tolerated. A large retrospective »

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key points

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Gallstones affect around 15% of adults in the UK.

Between 50 and 70% of patients with gallstones are asymptomatic at the time of diagnosis and only 10-25% of these individuals will go on to develop symptomatic gallstone disease. The vast majority (90-95%) of gallstones are cholesterol stones. To prevent gallstones, the European Association for the Study of Liver Disease recommends a healthy lifestyle and diet, regular physical activity and maintenance of an ideal body weight.

Obesity is associated with an increased risk of symptomatic gallstones.

There is also a strong independent association between cholesterol gallstones and type 2 diabetes. Other risk factors for cholesterol stones include female gender, pregnancy, oral hormone replacement therapy, advancing age, rapid weight loss, bariatric surgery, Crohn's disease and cirrhosis.

The most common symptom of gallstones is biliary colic.

This is a steady, pain in either the epigastrium or right upper quadrant (that may radiate to the interscapular region or right shoulder). It typically builds to a peak within 30 minutes, and lasts for between 30 minutes and 8 hours. It is frequently triggered by fatty foods and may be associated with nausea and vomiting but not fever or abdominal tenderness. A proportion of patients will present with atypical symptoms such as dyspepsia. Patients who undergo cholecystectomy for dyspepsia attributed to gallstones do not have a good clinical outcome.

Patients with symptoms suggestive of gallstones should

be offered liver function tests (LFTs) and an abdominal ultrasound. Patients with proven gallstones and uncomplicated biliary pain should be referred for routine laparoscopic cholecystectomy. It is imperative that a laparoscopic cholecystectomy should only be carried out when the bile duct is clear of stones. As ultrasound may fail to detect common bile duct stones, NICE recommends MRCP for patients who have a dilated bile duct and/or abnormal LFTs. Any patients found to have choledocholithiasis should have bile duct clearance with an ERCP prior to surgery. Bile duct clearance is also recommended for patients with incidental asymptomatic choledocholithiasis.

Cholecystitis is the most common complication of

gallstones and occurs in about 10% of patients with symptomatic gallstones. The presentation is similar to biliary colic and the pain typically lasts longer than 6 hours and is accompanied by fever and raised inflammatory markers. Examination may reveal a positive Murphy's sign.

Patients with choledocholithiasis can develop infection

of the biliary tree (cholangitis) with a risk of life-threatening bacteraemia and biliary sepsis. Patients classically present with pain, fever and jaundice (Charcot's triad), but this has low sensitivity and other diagnostic criteria have been proposed.

cohort analysis from Sweden found that patients who had duct clearance had half the risk of complications compared with those who did not (12.7% vs 25.3%).²⁷

The most common approach to bile duct clearance is ERCP performed using a side viewing endoscope. Commonly a biliary sphincterotomy ± sphincteroplasty (balloon dilatation of the sphincter) is performed to increase the size of the bile duct exit into the duodenum and stones are then removed using an extraction balloon or basket. The main risks of ERCP are bleeding (1.3%), perforation (0.6%), cholecystitis/cholangitis (1.4%) and post procedure pancreatitis (3.5-9.7%);²⁸ this should be a consideration if patients present to primary care with pain after their procedure.

Bile duct stones may also be cleared at the time of cholecystectomy with intraoperative ERCP or laparoscopic bile duct exploration and clearance. These methods are equally efficacious but there are a decreasing number of surgeons experienced at performing laparoscopic bile duct exploration and so preoperative ERCP is the more common approach in the UK.³

There are a cohort of predominantly elderly patients who become unwell from cholecystitis or cholangitis and may not be candidates for laparoscopic cholecystectomy. Traditionally, percutaneous gallbladder drainage performed in interventional radiology has been the next modality of choice for an acutely inflamed gallbladder that is not settling with antibiotics, but it is associated with a high rate of morbidity and complications.²⁹

Recently, internal drainage has been made possible by endoscopic ultrasound-guided drainage using lumen apposing metal stents sited to allow drainage of the gallbladder into the stomach or duodenum. One study suggests a much lower complication rate compared with percutaneous gallbladder drainage and favourable outcomes.³⁰

The treatment of gallstone pancreatitis is supportive. It is beyond the scope of this article and has been covered by an earlier article in this journal.³¹ Gallstone pancreatitis is a strong indication for cholecystectomy and a multicentre, randomised controlled trial showed that same admission cholecystectomy reduced the rate of recurrent gallstone related complications in patients with mild gallstone pancreatitis with a very low risk of postoperative complications. The EASL suggests cholecystectomy should be performed during the same admission as the initial pancreatitis episode.³

CONCLUSIONS

Gallstones are a very common cause of patients presenting to primary care. Most patients will remain asymptomatic and can be reassured if their gallstones are detected incidentally. However, a proportion will go on to develop complications some of which can be very severe. Symptomatic patients should be referred for consideration of cholecystectomy and any patients found to have choledocholithiasis should have bile duct clearance with an ERCP.

Patients at risk of gallstone development may have risk factors that also increase their operative risk for cholecystectomy such as obesity and should be encouraged to reduce their risk through lifestyle modification.

Competing interests

Dr Gavin Johnson has done consultancy educational work for Boston Scientific, Mylan, Pentax, Olympus and Cook Medical. The other authors have no competing interests.

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Useful information

Clinical guidelines on gallstone disease

EASL

easl.eu/publication/prevention-diagnosis-and-treatment-of-gallstones

NICE

www.nice.org.uk/cg188

For patients

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