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What you need to know about gallstone disease

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Abstract

Gallstone disease is becoming increasingly common in the UK, with one in six people developing gallstones and over 100 000 cholecystectomies being performed annually. The gallbladder stores bile produced by the liver and, in the presence of fat in the stomach, releases bile into the duodenum to promote the emulsification and absorption of fats and fat-soluble vitamins from the small bowel. Although most people with gallstones remain asymptomatic throughout their lifetime, approximately 20% go on to develop complications of varying severity, ranging from biliary colic to ascending cholangitis, which can be fatal if left untreated. Ultrasound is the most reliable investigation for confirming gallstone disease. Cholecystectomy provides definitive treatment of symptomatic disease and is usually offered as a laparoscopic, day-case procedure. This article explores the pathogenesis and management of gallstone disease.

Key words: Cholangitis; Cholecystectomy; Cholecystitis; Gallbladder; Gallstones; Pancreatitis

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Introduction

Gallstone disease is one of the most common causes of abdominal pain in patients presenting to hospital as an emergency. Over 100 000 cholecystectomies are performed annually in the UK. The prevalence of gallstones is approximately one in six adults, but fewer than 20% develop gallstone-related complications (Rance and Jones, 2016). This article explores the pathogenesis and management of gallstone disease.

Anatomy

The gallbladder is a pear-shaped, distensible, thin-walled sac that sits within the cystic fossa on the under surface of liver segments IVb and V. The gallbladder is split into regions termed the fundus, body and neck; the latter opening into the cystic duct (Figure 1). The cystic duct joins with the common hepatic duct (fusion of the right and left hepatic ducts) to form the common bile duct. The common hepatic duct runs into the porta hepatis, which also consists of the hepatic artery (which gives the terminal cystic artery to the gallbladder) situated to the left and with the portal vein posteriorly. The common bile duct is joined by the main pancreatic duct and opens on the medial aspect of the second part of the duodenum at the sphincter of Oddi (Mahadevan, 2020).

The surface marking of the gallbladder fundus corresponds to the point at which the lateral border of the right rectus abdominis meets the costal margin at the level of the right ninth intercostal cartilage and in the vertebral level of L1.

Pathophysiology

The gallbladder functions as a store containing approximately 50 ml of bile. The I-cells of the duodenum release cholecystokinin in the presence of fat which stimulates gallbladder contraction and release of bile into the duodenum. Bile promotes emulsification and absorption of fat and fat-soluble vitamins from the small bowel.

Bile is a complex solution of water, bilirubin (byproduct of red blood cell degradation), phospholipids, cholesterol, bile salts and other minerals. Imbalance in any of these constituents leads to supersaturation, promoting crystal precipitation and ultimately gallstones. Gallstone formation is enhanced by gallbladder stasis. In the west, excess levels of cholesterol in the blood lead to cholesterol stone formation (80% of all gallstones; Table

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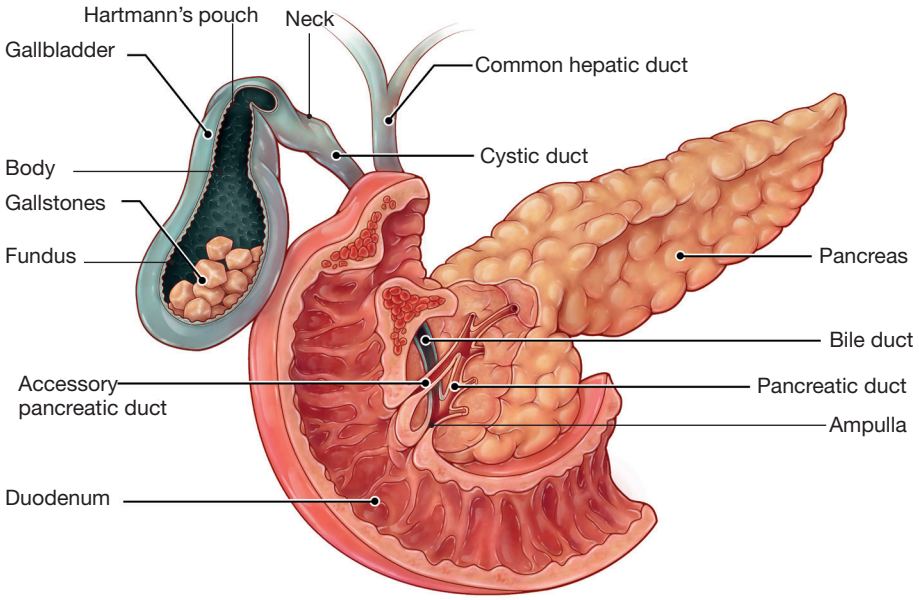

Figure 1. Anatomy of the gallbladder and biliary ducts.

Table 1. Mnemonic for risk factors for development of cholesterol gallstones: the 6 Fs
Female
Fat (obese)
Fertile
Fair (Caucasian)
Forties (age)
Family history

1 shows risk factors for development of cholesterol stones). Black pigment stones (10% of stones) are formed from an excess of unconjugated bilirubin, for example in patients with haemolytic diseases (sickle cell anaemia, thalassaemia, hereditary spherocytosis) and cirrhosis. Brown pigment stones (<5% of stones) form as a result of biliary infection (ie *Escherichia coli* and *Klebsiella* spp.) leading to the formation of unconjugated bilirubin, which is insoluble. These may develop within the bile ducts or gallbladder (Beckingham, 2001).

Bile acids are conjugated in the liver to become water soluble. Following secretion into the gastrointestinal tract, 95% of bile salts are reabsorbed via the enterohepatic circulation (Figure 2).

Risk factors

Both genetic and environmental factors are involved in the pathogenesis of gallstone formation, occurring three times more commonly in first-degree relatives (Lammert and Sauerbruch, 2005). The prevalence is highest in native Americans, followed by white European and American populations.

Diets high in fats and carbohydrates, obesity, type 2 diabetes mellitus and dyslipidaemia (low levels of high-density lipoprotein, high levels of triglycerides) are strong risk factors for formation of cholesterol gallstones. Cholesterol supersaturation is also seen with drugs that enhance cholesterol secretion (eg fibrates), rapid weight loss in obese patients and total parenteral nutrition (as a result of gallbladder hypomotility, high lipid levels and reduced enterohepatic circulation).

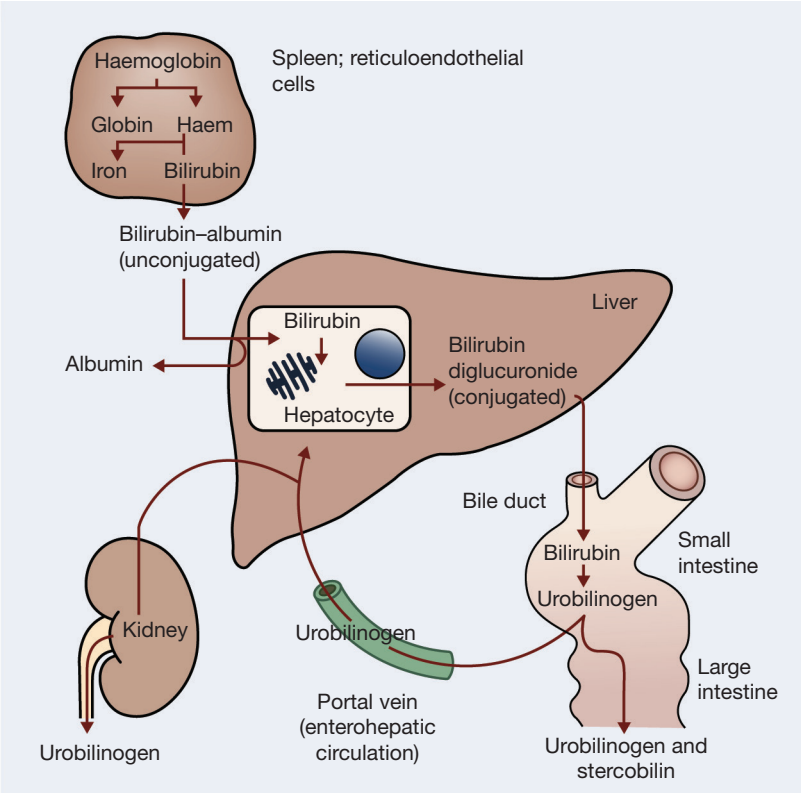

Figure 2. Enterohepatic circulation.

Gallstone disease shows a female preponderance (10:1 female-to-male ratio). High oestrogen levels are associated with increased secretion of cholesterol, reduced secretion of bile salts and reduced contraction of the gallbladder (Wong et al, 2019).

Presentation

While gallstones are common in the UK, the majority of patients remain asymptomatic throughout their life. The annual risk of patients with asymptomatic gallstones developing symptoms is 1–4%, but once symptoms develop the risk of symptom recurrence is 50% (Beckingham, 2001).

Biliary colic

Pain is the most common presenting complaint in patients with symptomatic gallstone disease. Pain is ischaemic in nature, resulting from gallbladder wall contraction, often against a stone lodged within the gallbladder neck or cystic duct. Contrary to the term 'colic', pain is usually constant, lasting for several hours, and is felt in the epigastrium and right upper quadrant. Attacks may be precipitated by fatty meals and accompanied by nausea and vomiting. Simple analgesia usually settles an attack and a low-fat diet may reduce the frequency of attacks (Ciaula et al, 2019), although cholecystectomy remains the definitive treatment.

Acute cholecystitis

Acute cholecystitis is differentiated from biliary colic by the presence of an associated inflammatory response. Persistent cystic duct obstruction causes an increase in gallbladder glandular secretion and subsequent distention which may trigger inflammation and in turn compromise the vascular supply to the gallbladder. Secondary infection may then ensue.

Clinically, acute cholecystitis manifests as right upper quadrant tenderness, raised levels of inflammatory markers (white cell count and C-reactive protein) and sonographic features of inflammation (see investigations). This triad forms the basis of the Tokyo guidelines diagnostic criteria (Yokoe et al, 2018). Liver function tests may also be mildly deranged.

Murphy's sign refers to cessation of inspiration during right upper quadrant palpation owing to an inflamed gallbladder contacting the overlying peritoneum on descent. A pus-filled gallbladder (empyema) may present with swinging pyrexia, while gangrene and perforation cause systemic upset and generalised peritonitis.

Treatment includes resuscitation with intravenous fluids, analgesia and antibiotics. Non-steroidal anti-inflammatory drugs increase the speed of recovery and prevent progression if given early before bacterial infection ensues (Fraquelli et al, 2016). Most guidelines favour early laparoscopic cholecystectomy in patients with acute cholecystitis. In very unwell or comorbid patients with gallbladder empyema, drainage via percutaneous cholecystostomy may provide temporary source control.

Common bile duct stones (choledocholithiasis)

Stones may migrate from the gallbladder via the cystic duct into the common bile duct. Non-obstructing stones may not cause symptoms or may pass into the duodenum spontaneously and are seen in approximately 15% of patients with symptomatic gallstone disease. Pain is classically felt in the epigastrium and may radiate to the back owing to the retroperitoneal position of the distal common bile duct.

Obstruction of the flow of bile into the bowel classically presents with pale stools (lack of brown pigment; stercobilin – **Figure 2**), dark urine (increased levels of conjugated bilirubin in the urine), yellow skin and/or eyes (icterus) and pruritis (Copelan and Kapoor, 2015). Liver function tests may demonstrate an obstructive (post-hepatic) pattern with raised levels of conjugated bilirubin and alkaline phosphatase, and normal or mildly raised levels of transaminases. Common bile duct stones are removed either via surgical exploration or via endoscopic retrograde cholangiography.

A rare cause of biliary obstruction is extrinsic compression of the common hepatic duct by an impacted gallstone within the gallbladder or cystic duct with associated inflammation (Mirizzi syndrome) (Wang and Afdhal, 2021).

Pancreatitis

Approximately 5% of patients with gallstones develop acute pancreatitis. Small stones or microlithiasis pose a higher risk of acute pancreatitis developing because they are more easily able to pass into the common bile duct and obstruct the pancreatic duct. The resultant increase in pancreatic pressure damages ductal and acinar cells, causing proteolytic enzyme activation and subsequent autodigestion of the pancreas with associated inflammation. Treatment in the acute phase is largely supportive, with particular attention to fluid balance, nutritional status and analgesia. Organ support may be required in severe cases. A raised serum amylase level of more than three times the upper limit of normal is highly suggestive of pancreatitis. An urgent endoscopic retrograde cholangiography and sphincterotomy is indicated only in patients with concurrent cholangitis or persistent biliary obstruction. UK guidelines recommend cholecystectomy within 2 weeks of presentation to prevent recurrence, as long as the patient is fit for surgery (Working Party of the British Society of Gastroenterology et al, 2005). Endoscopic retrograde cholangiography with sphincterotomy may also be used as definitive management to prevent further attacks of gallstone pancreatitis in patients unfit for cholecystectomy.

Ascending cholangitis

Bile duct stasis as a result of common bile duct obstruction permits ascending infection from the duodenum. Common organisms are Gram-negative, enteric bacteria (ie *E. coli* (most common), *Klebsiella* spp., *Enterobacter* spp.), or less commonly Gram-positive bacteria (ie *Enterococcus* spp.) (Vaishnavi, 2013). Patients may present with a triad of right upper quadrant pain, jaundice and fever (Charcot's triad). Early intervention with intravenous antibiotics, fluid replacement and bile duct decompression via endoscopic retrograde cholangiography is crucial to reduce mortality.

Gallstone ileus

A cholecysto-enteric fistula occurs when a gallstone erodes through the gallbladder wall and into the enteric system, usually the duodenum, following episodes of chronic

inflammation. Passage of larger stones into the small bowel may then lead to mechanical blockage (especially at points of narrowing such as the ileocaecal valve). The term ileus is thus a misnomer. Gallstone ileus accounts for 1% of all cases of small bowel obstruction. Patients will typically have a longstanding history of gallstone disease and present with acute onset of abdominal distension, nausea and vomiting, and absolute constipation. It has a high mortality of approximately 20% owing to delayed diagnosis (Lassandro et al, 2004). Emergency laparotomy with enterotomy and stone extraction is indicated.

Investigation

Ultrasound

Transabdominal ultrasound is the gold standard radiological test for diagnosing gallstones, with a 95% sensitivity for stones >2 mm in size. Prescanning fasting increases sensitivity owing to gallbladder distension. Wall thickening and pericholecystic fluid indicate acute cholecystitis (Table 2).

Less than 50% of common bile duct stones are seen on transabdominal ultrasound. However, dilatation of the bile duct suggests obstruction of the common bile duct (Lassandro et al, 2004).

Magnetic resonance cholangiopancreatography

Magnetic resonance cholangiopancreatography is highly sensitive for choledocholithiasis (93% sensitivity and 94% specificity) and accurately delineates the biliary anatomy (Kaltenthaler et al, 2004). Contraindications to magnetic resonance imaging include patients with older models of pacemaker, ferrous metal implants or foreign bodies, metallic fragments in eye, metallic brain clips and severe claustrophobia.

Endoscopic ultrasound

Endoscopic ultrasound offers improved visualisation of the gallbladder, biliary tree and pancreas compared with transabdominal ultrasound. However, it is more invasive, requiring endoscopy and intubation of the stomach and duodenum with the probe. Endoscopic ultrasound is indicated for the detection of small stones (microlithiasis), such as in patients with suspected biliary pancreatitis but no evidence of gallstones on transabdominal ultrasound.

Computed tomography

Computed tomography is less sensitive at detecting gallstones than ultrasound and magnetic resonance cholangiopancreatography as most gallstones do not contain calcium and hence are not radio-opaque. However, computed tomography may be useful in cases of diagnostic doubt or where pancreatic or biliary malignancy is suspected (such as obstructive jaundice in the absence of gallstones).

Endoscopic retrograde cholangiography

Endoscopic retrograde cholangiography provides both diagnostic and therapeutic measures for bile duct obstruction. It allows direct visualisation of the ductal anatomy and has a 95% sensitivity and specificity for detecting common bile duct stones. However, endoscopic retrograde cholangiography is invasive, with risks including bleeding, perforation (1%), infection and pancreatitis (5%) (James and Baron, 2021).

Table 2. Ultrasound sonographic features of acute cholecystitis

Sonographic Murphy's sign (most sensitive)
Gallbladder wall thickening (>3 mm)
Pericholecystic fluid
Lack of movement of impacted echogenic gallstones
Gallbladder distension (less sensitive)

Management of gallstone disease

Cholecystectomy

National Institute for Health and Care Excellence (2014) guidelines suggest that patients with asymptomatic gallstones do not require any intervention. For symptomatic disease, cholecystectomy provides definitive treatment and is usually offered as a laparoscopic, day-case procedure.

Acute cholecystectomy as part of the management of acute cholecystitis is safe and cost effective with reduced total length of hospital stay. National Institute for Health and Care Excellence (2014) guidelines suggest operating within 7 days of symptom onset. Numerous trials show that complication rates are similar to those of interval cholecystectomy after 6 weeks (once inflammation has settled) (Khan et al, 2014). Table 3 details the operative steps for a laparoscopic cholecystectomy.

Complications of cholecystectomy include bleeding, infection (superficial or deep) and pain. Approximately 10% of patients will have ongoing symptoms (post-cholecystectomy syndrome), likely as a result of alternative pathology mimicking biliary pain. Less common complications include bile leak, retained or dropped stone, and port site hernia. Iatrogenic injury to the bowel, bladder, liver or common bile duct is rare (approximately 1:300), but with significant consequences. Management of common bile duct injury includes insertion of drains and transfer to a tertiary centre for reconstruction with hepatico-jejunostomy.

Alternative treatments

Non-surgical approaches for the management of gallstones, including extracorporeal shockwave lithotripsy and oral dissolution therapy with ursodeoxycholic acid, are rarely used owing to low success and high recurrence rates.

Management of common bile duct stones

Management of common bile duct stones can be achieved either preoperatively or intraoperatively. Preoperative management includes diagnosis via magnetic resonance cholangiopancreatography or endoscopic ultrasound, followed by endoscopic therapeutic intervention known as endoscopic retrograde cholangiopancreatography. Identification of common bile duct stones via intraoperative cholangiography or laparoscopic ultrasound, proceeding directly to intraoperative bile duct clearance, prevents unnecessary delays in management, reduces costs and minimises use of magnetic resonance imaging or endoscopic ultrasound resources (Association of Upper Gastrointestinal Surgery of Great Britain and Ireland, 2015).

Table 3. Laparoscopic cholecystectomy: operative steps

1. Laparoscopic port access and pneumoperitoneum achieved by insertion of 10 mm umbilical, 5 or 10 mm subxiphoid, and 2x5 mm right subcostal ports
2. Retract the gallbladder fundus superiorly over the liver
3. Identify and dissect the hepatocystic triangle to achieve ‘critical view of safety’ as defined by: a. Clearance of fatty and fibrous tissue within the hepatocystic triangle b. Presence of only two structures (cystic duct and artery) entering the gallbladder c. Separation of the lower third of the gallbladder from the cystic fossa
4. Once the cystic artery and duct are identified, these are clipped and divided
5. Dissect the remainder of the gallbladder from the liver bed
6. Place the gallbladder into a specimen pouch and remove it via the umbilical or epigastric port
7. Ensure haemostasis
8. Close 10 mm port sites and skin with absorbable sutures

Conclusions

With gallstone disease becoming more prevalent in the western world, it is increasingly important to be aware of how gallstone disease presents and how it is subsequently diagnosed and managed. This article explores the anatomy of the biliary system, pathophysiology of gallstone formation, as well as the presentation and management of gallstone disease. Once gallstones become symptomatic, the only definitive management to prevent recurrence of symptoms or complications is with surgical intervention to remove the gallbladder (cholecystectomy).

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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Key points

- Gallstones are a common cause of acute abdominal pain, although the majority of cases remain asymptomatic.
- Biliary colic is characterised by pain in the right upper quadrant and epigastrium, typically after ingestion of fatty food, and can last several hours.
- Cholecystectomy is the definitive management for symptomatic gallstone disease; patients with asymptomatic gallstones do not require surgery.
- Cholecystectomy in patients with acute cholecystitis is safe and cost effective providing it is undertaken within 7 days of symptom onset.
- Pancreatitis is managed with analgesia, zealous fluid balance and nutritional support. In pancreatitis secondary to gallstones, early cholecystectomy is advised to prevent recurrent episodes.
- Common bile duct stones are managed by preoperative endoscopic retrograde cholangiography or intraoperative bile duct exploration.

Curriculum checklist

This article addresses the following requirements from the general internal medicine curriculum:

- Managing an acute specialty-related take
- Providing continuity of care to medical inpatients, including management of comorbidities and cognitive impairment
- Managing patients in an outpatient clinic, ambulatory or community setting, including management of long-term conditions.

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