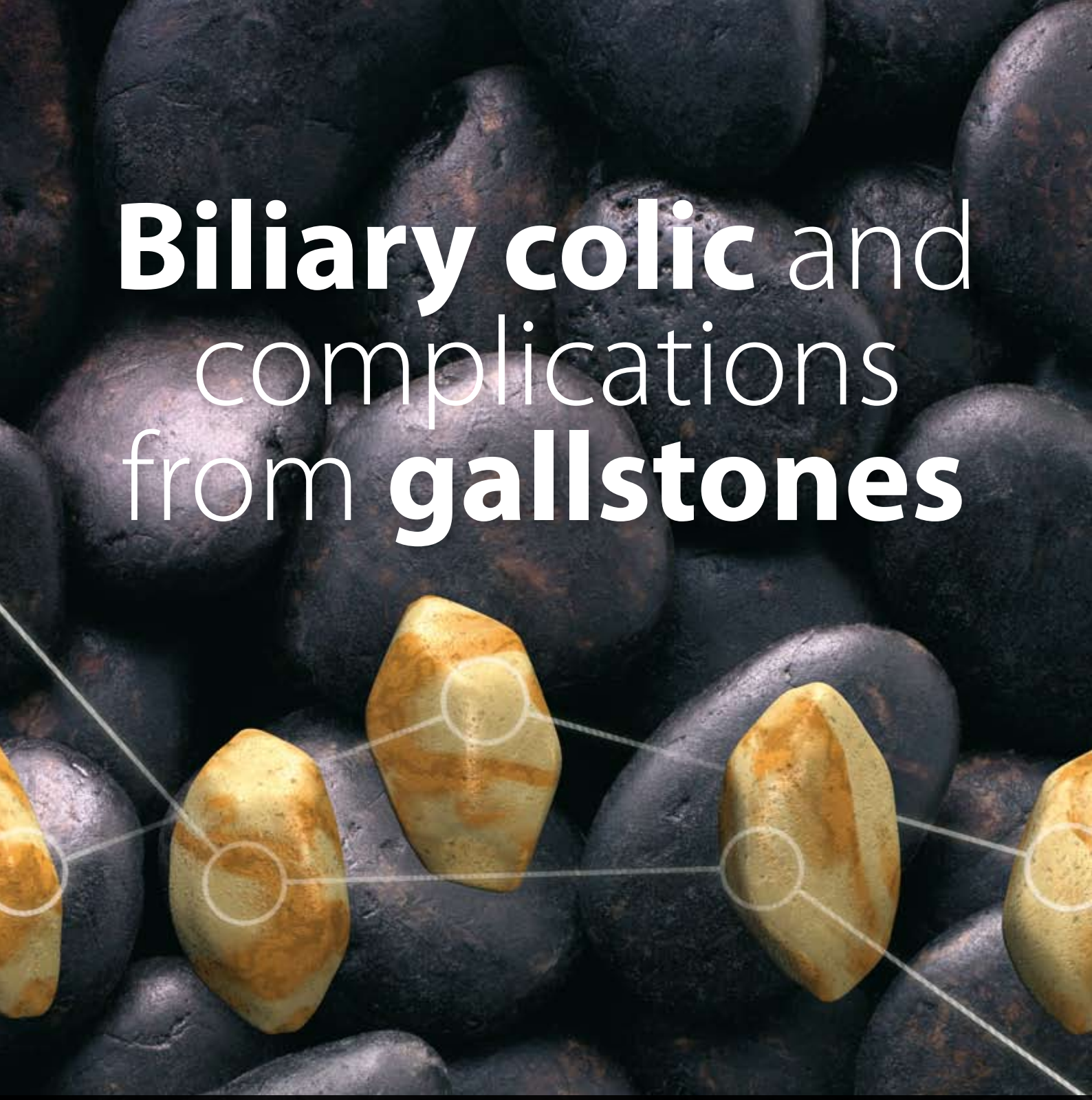

Biliary colic and complications from **gallstones**

Gallstones are common among the general population, but because they rarely cause symptoms many people are unaware of their presence. Over a ten-year period, approximately one-third of people with gallstones will develop the painful symptoms of biliary colic. This can be a precursor to more serious conditions, such as acute cholecystitis and pancreatitis that require acute advanced endoscopic or surgical assessment. The presence of upper abdominal pain, despite normal physical examination and blood test results, is consistent with uncomplicated biliary colic. An ultrasound should be arranged for all patients with features suggestive of biliary colic to confirm a diagnosis. Patients with biliary colic are generally managed in the community with non-steroidal anti-inflammatory drugs (NSAIDs) and lifestyle advice while awaiting assessment for laproscopic cholecystectomy.

Gallstones and their associated complications

Cholelithiasis, the presence of gallstones in the gallbladder, is estimated to occur in 10 – 15% of the adult population in the United States.[1] In New Zealand, a small study estimated that 20% of the New Zealand population aged 30 to 75 years had cholelithiasis.[2] Most people with cholelithiasis are asymptomatic, but over a ten year-period approximately one-third will develop symptoms.[3] Symptoms are usually caused by blockage of the cystic duct by a gallstone or by migration of a gallstone into the common bile duct. Blockage of the cystic duct causes pressure within the gallbladder to rise, resulting in symptomatic cholelithiasis that is usually accompanied by a distinctive pattern of abdominal pain, referred to as biliary colic. Blockage of the common bile duct causes a similar pain, but may be accompanied by jaundice, pancreatitis or cholangitis (Page 30).

Approximately 70% of gallstones are cholesterol stones, i.e. more than half the stone is formed from cholesterol.[4] These stones form when bile becomes supersaturated with cholesterol, following increased secretion of cholesterol from the liver or when production of bile salt or lecithin (an emulsifying fatty substance) decreases.[4] Cholesterol microcrystals then precipitate from biliary sludge within the gallbladder.[1] Black pigment stones are the other significant type of gallstone found among people in Western countries.[4] These are made up of calcium bilirubinate and are related to haemolytic disorders with an increased bilirubin load, and occasionally cirrhosis.

Cholelithiasis is formally diagnosed by abdominal ultrasound, and in symptomatic patients, is treated surgically with cholecystectomy.[4] Patients with uncomplicated episodes of biliary colic can generally be managed in the community with analgesics and lifestyle advice while they wait for surgery.

Risk factors for gallstone formation

Factors associated with an increased risk of cholelithiasis include:[4]

- Increasing age
- Increasing body mass
- Female sex
- Pregnancy (see: "Cholelithiasis in women who are pregnant", Page 32)
- Medicines, e.g. oral contraceptives, fibrates
- Family history
- Rapid weight loss, e.g. following bariatric surgery
- Haemolytic disorders, e.g. haemolytic anaemia

Gallstones are more prevalent in people who are obese because increasing body mass is associated with an increased production of cholesterol by the liver.[4] Periods of rapid weight loss are also associated with gallstone formation and people are more likely to become symptomatic during this time. This is possibly due to an increase in the relative amount of cholesterol in the gallbladder and reduced gallbladder contractility.[4] In contrast, people who take statins long-term are less likely to undergo surgery for biliary colic. One study found that statin use for periods of five years or more was associated with a decreased risk of cholecystectomy.[5] Exercise can also reduce a patient's likelihood of developing gallstones and moderate physical activity is reported to prevent gallstone formation independently of body mass.[6]

The higher prevalence of cholelithiasis among females is most likely related to oestrogen increasing biliary secretion of cholesterol and progesterone reducing bile acid secretion by increasing gallbladder stasis.[7] The risk of gallstone formation in females is increased by taking oral contraceptives.[8]

People who have a first-degree relative with cholelithiasis are almost 4.5 times more likely to develop gallstones.[9] Diabetes, hypertriglyceridaemia, Crohn's disease, cirrhosis and conditions that cause the bile duct to become blocked, or procedures that cause bile salt loss, e.g. ileal resection, are also associated with cholelithiasis.[4]

Diagnosing biliary colic

Biliary colic typically refers to a steady pain, rather than a series of "colicky" waves that might be expected from the term.[4] The pain originates in the right upper quadrant or epigastric area and can radiate around to the subscapular region.[8] The pain will typically last for more than 30 minutes with an upper limit of six hours, and is unaffected by movement, body position or defaecation.[4] The patient will often be nauseated and may vomit.[8] Episodes of biliary colic often occur following a meal

or at night, and after an initial episode, recurrence is common and may occur within hours.[4] In some patients, however, recurrence may occur years later.[4]

Atypical symptoms of biliary colic are not unusual and include: chest pain, belching (eructation), rapid satiety, dyspepsia and non-specific abdominal pain.[4]

Choledocholithiasis (see glossary) can cause pain that is indistinguishable from biliary colic but may be accompanied by obstructive jaundice, cholangitis or acute pancreatitis.[11] The risk of bacteraemia is also increased in patients with choledocholithiasis as increased biliary pressure can force bacteria from the bile duct into the blood stream of the liver.[10]

Consider differential diagnoses

As gallstones are prevalent, and most people who have them are asymptomatic, their presence does not necessarily mean that a patient's abdominal pain is due to cholelithiasis.

Gastro-oesophageal reflux disease (GORD), peptic ulcer disease, non-ulcer dyspepsia, hepatitis, right-sided pyelonephritis, nephrolithiasis, appendicitis, pancreatitis, bowel obstruction, bowel ischaemia, right-sided pneumonia, abnormal aortic dissection and an atypical presentation of ischaemic heart disease are among the many conditions that may cause upper abdominal pain. Irritable bowel syndrome should also be considered, particularly in patients with a longer history of symptoms who report pain that is relieved by defaecation and

A glossary of the complications of cholelithiasis

1. **Acute cholecystitis** is the most frequent complication of symptomatic cholelithiasis and is characterised by inflammation of the gallbladder wall.[6] The risk of this is increased in patients with larger gallstones that are more likely to be trapped within the gallbladder. Gangrenous cholecystitis and perforation of the gallbladder are serious complications of acute cholecystitis.[13] In severe cases acute cholecystitis can be fatal.

2. **Chronic cholecystitis** is also common and results from recurrent or relapsing bouts of acute cholecystitis. Rare but serious complications of chronic cholecystitis include:
   a) **Mirizzi syndrome**, which is an unusual cause of obstructive jaundice occurring when a large stone becomes impacted in Hartman's pouch causing extrinsic compression and eventual erosion of the common hepatic duct
   b) **Gallstone ileus**, which occurs when there is mechanical obstruction due to the impaction of a large gallstone at the ileocaecal valve, often after spontaneously eroding into the small bowel via a cholecystoenteric fistula
   c) **Gallbladder cancer**, which in most cases develops from long-term cholelithiasis and chronic cholecystitis. Patients are often asymptomatic until the cancer develops. Most early gallbladder cancers are diagnosed incidentally following cholecystectomy for cholelithiasis.

3. **Choledocholithiasis** is the migration of gallstones from the gallbladder into the common biliary duct. This is more likely to occur in patients with small gallstones because these can pass with greater ease through the cystic duct.[6] There are three main clinical consequences of choledocholithiasis:
   a) **Obstructive jaundice**, which occurs when a bile duct stone obstructs the flow of bile into the duodenum. Patients will typically present with biliary colic accompanied by jaundice, dark urine, pale stools and pruritus.
   b) **Acute pancreatitis**, which is caused by temporary obstruction to the pancreatic duct during passage of a bile duct stone through the ampulla of Vater into the duodenum. It can range in severity from mild and transient to life-threatening.
   c) **Ascending cholangitis**, which occurs when bile in an obstructed bile duct becomes infected, often from bacteria embedded in the matrix of a gallstone within the bile duct.[10]

pain that is more constant over 24 hours.[8] Colorectal cancer should be considered in patients, particularly those aged over 50 years and those with a family history of this malignancy.

For further information, see: "Surveillance of people at increased risk of colorectal cancer", BPJ 44 (May, 2012).

Examining the patient

Patients with uncomplicated biliary colic will typically display pain in the right upper quadrant and epigastrium, and on examination may display voluntary guarding.[4] Severe and ongoing pain and rebound tenderness on examination suggest that the patient has developed acute cholecystitis, the suspicion of which should be increased if the patient displays a positive Murphy's sign.

To assess for a positive Murphy's sign ask the patient to inspire deeply while palpating the right subcostal region. Increased discomfort in patients with a positive sign is due to inflammation of the peritoneum overlying the gallbladder and therefore palpation causes the patient to "catch" their breath. However, a negative sign does not necessarily exclude cholecystitis and should be interpreted with caution, particularly in older patients.[12]

Ascending cholangitis is a dangerous condition identified clinically by Charcot's triad of jaundice, fever and right upper abdominal pain.[10] Mirizzi syndrome is usually diagnosed after imaging a patient with long-term gallstone disease. The presentation of Mirizzi syndrome can vary greatly but usually includes jaundice or abnormal liver function tests (LFTs), associated with dilated intra-hepatic ducts on ultrasound with a large stone in Hartman's pouch.

Investigating biliary colic

Routine testing of patients with suspected biliary colic should include:

- Full blood count (FBC)
- Liver function tests (LFTs)
- Serum creatinine
- CRP
- Serum amylase
- Urine dipstick

In patients with uncomplicated biliary colic, FBC, LFTs and markers of pancreatic injury, i.e. serum amylase, should be within the normal range.[4] Leukocytosis and an elevated CRP are typical in patients with acute cholecystitis, but liver enzymes are either normal or only marginally elevated. Markedly elevated liver enzymes are suggestive of choledocholithiasis, which may be complicated by acute pancreatitis (elevated serum amylase) or cholangitis, indicated by Charcot's triad. Gamma glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) levels will be raised in 94% and 91% respectively of patients with choledocholithiasis.[10] Serum amylase is elevated transiently in the majority of patients with acute pancreatitis. Transient elevation of aspartate aminotransferase (AST) and ALT in combination with acute biliary pain and elevated amylase is strongly suggestive of passage of a bile duct stone. If the patient has atypical chest pain then an ECG should be performed and a troponin test requested to help exclude a cardiac cause for the pain.

Ultrasound is the gold-standard diagnostic test for biliary colic

Abdominal ultrasound is used to confirm a diagnosis of biliary colic in all patients before a laparoscopic cholecystectomy is performed. Local guidelines may vary, but usually recommend a prompt abdominal ultrasound (within five days) for patients with:

- Jaundice and abnormal LFTs
- Significant, persistent or recurrent upper quadrant pain

A routine ultrasound (within four weeks) should be arranged for patients with characteristic abdominal pain and laboratory results that are normal or mildly abnormal, but without jaundice.

Red-flags for acute referral to hospital for surgical assessment include:

- Biliary colic that cannot be effectively controlled with analgesia
- Obstructive jaundice
- Suspected acute cholecystitis
- Cholangitis
- Acute pancreatitis

Abdominal ultrasound can detect approximately 95% of gallstones as well as being able to detect complications of gallstones, e.g. inflammation of the gallbladder wall or obstruction of the common bile duct.[4] Ultrasound can also identify biliary sludge in some patients, which is seen as layering within the gallbladder.

The sensitivity of ultrasound for detecting gallstones decreases as the patient's body mass increases and may also be affected by increased bowel gas, which can occur in patients with acute complications, such as pancreatitis. The sensitivity of ultrasound for bile duct stones is approximately 60% and

patients with dilated bile ducts or other suspicious features on ultrasound will usually require further investigation.

Magnetic resonance imaging (MRI) will detect bile duct stones in approximately 90% of patients with choledocholithiasis.[10]

Endoscopic retrograde cholangiopancreatography (ERCP) may be used to diagnose and treat common bile duct stones and to clear the common bile duct prior to or after laproscopic cholecystectomy in patients with cholelithiasis complicated by choledocholithiasis.[14] ERCP requires the patient to be sedated and involves fluoroscopy and may include biliary sphincterotomy.

Managing biliary colic in primary care

Patients who have had an episode of uncomplicated biliary colic may be managed in the community while they wait for a definitive diagnosis and surgical assessment. During this time recurrent bouts of biliary colic may occur.[17]

Lifestyle management

The patient's dietary history may indicate foods that are triggers for biliary colic which can then be avoided, e.g. fatty food and high-fat dairy products. A high-fibre diet that contains nuts and is low in saturated fat is associated with a reduced risk of gallstone formation and it is possible that making dietary changes will improve the patient's symptoms.[6] Paradoxically, for patients on a low-calorie diet the consumption of 10 g of fat per day has been shown to prevent gallstone formation,

Cholelithiasis in women who are pregnant

During pregnancy, physiological changes increase the likelihood of gallstone formation. These include: increased gallbladder stasis, increased bile production by approximately 50%, elevated levels of cholesterol, and reduced levels of the bile acid chenodexycholic acid.[1] The risk of gallstones forming also increases with the number of pregnancies a woman has had.[1] Biliary colic is estimated to occur in three to five women per 1000 pregnancies.[1] The most important predictors of biliary colic during pregnancy are a personal history of biliary colic, increased body mass index (BMI) and reduced exercise.[1]

The symptoms of biliary colic in women who are pregnant are the same as for other patients, although pregnancy-related causes of abdominal pain must be considered, particularly in later pregnancy, e.g. pre-term labour, placental abruption, acute fatty liver of pregnancy, severe pre-eclampsia and HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome. Acute pancreatitis during pregnancy is a rare but potentially severe complication of choledocholithiasis that is associated with high maternal mortality rates.[1] Pregnant women with suspected biliary colic or acute pancreatitis are best managed by immediate referral to an emergency department.

Initial treatment of biliary colic in pregnant women generally involves temporary fasting and administration of intravenous fluids, analgesia and antibiotics, if signs of infection are present. The goal of management is to defer invasive procedures, if possible.[1]

Although in most circumstances NSAIDs are the recommended choice for managing pain from biliary colic, they should generally be avoided during pregnancy unless the benefit outweighs the risk.[15] NSAIDs are associated with adverse effects on foetal development early in pregnancy and an increased risk of miscarriage or premature closure of the ductus arteriosus later in pregnancy.[15, 16] Oral morphine can be used short-term, if required, for moderate to severe pain during pregnancy.[15]

Occasionally, surgical intervention is needed when a conservative approach is not effective. Where possible, this is performed during the second trimester.[1] During the first trimester there is an increased risk to the foetus due to surgical general anaesthesia and during the third trimester there is an increased risk of uterine damage and the enlarged uterus can make access to the gallbladder difficult.[1] During the post-partum period bile rapidly reverts back to pre-pregnancy composition and some women will have spontaneous resolution of cholelithiasis.[1]

most likely by promoting gallbladder emptying.[6] Coffee and moderate amounts of alcohol have also been suggested by some researchers to have a protective effect against biliary colic.[6] Coffee is known to affect a number of processes involved in gallstone formation, including enhancing gallbladder contractility and decreasing cholesterol crystalisation in bile.[18]

NSAIDs are the first-line analgesic

NSAIDs are generally the preferred class of analgesia for biliary colic in patients with severe pain and those treated in the Emergency Department. However, there are a limited number of studies assessing the comparative effectiveness of analgesics in the treatment of biliary colic. In particular there are no studies assessing the effectiveness of combinations of analgesics, e.g. NSAIDs with opioids or NSAIDs with anti-spasmodics. In practice it may be necessary to provide multiple analgesics to patients who are in severe pain.[3]

Before prescribing NSAIDs for upper abdominal pain consider if the patient's pain may have another cause, e.g. peptic ulcer disease, for which NSAIDs are contraindicated.

Diclofenac injectable preparation is indicated for rapid onset pain relief in patients with biliary colic:[15]

- This can be given as diclofenac 75 mg (3 mL) injection, deep into the upper outer quadrant of the gluteal muscle, repeated once (may be given 30 minutes later if required, in the contralateral muscle)
- It may also be combined with oral diclofenac, 75 mg, to a maximum total dose of 150 mg, daily, for a maximum of two days
- Diclofenac suppositories may be considered as an alternative route of administration for patients unable to tolerate the oral or intramuscular route

Diclofenac is often the first-line NSAID for patients with biliary colic because of its speed of onset, when given intramuscularly, and its availability. Ten diclofenac 50 mg suppositories and five 75 mg injections are available fully subsidised on a PSO for general practices to have available for acute administration.

Oral ibuprofen, 200 – 400 mg, three to four times daily, or naproxen 250 – 500 mg, twice daily, may be considered as an alternative for subsequent bouts of biliary colic in some patients as these NSAIDs are associated with a lower cardiovascular risk than diclofenac.[15, 19] For example, diclofenac is contraindicated in patients who have had a myocardial infarction in the past 12 months.[19]

A review of eleven studies involving over 1000 patients found that NSAIDs (mainly diclofenac 50 – 75 mg) were more effective at controlling the pain of biliary colic than anti-spasmodic medicines, e.g. hyoscine butylbromide, and were equally as effective as opioids (mainly pethidine).[3] NSAIDs may also halt the progression of biliary colic to cholecystitis and other complications by limiting the production of prostaglandins.[6] NSAIDs were found to reduce the overall risk of short-term complications, i.e. jaundice, acute cholangitis, acute cholecystitis and acute pancreatitis, by approximately half compared to placebo.[3] Patients who were potentially at increased risk of the adverse effects of NSAIDs were excluded from this study, e.g. patients aged over 65 years, patients with diabetes or other systemic co-morbidities.[3]

NSAIDS may not be the most appropriate analgesic for some patients with biliary colic, e.g. patients with a history of peptic ulcer. For these patients other analgesics such as codeine and paracetamol or morphine may need to be considered (see below).

For further information see: "Non-steroidal anti-inflammatory drugs (NSAIDs): Making safer treatment choices", BPJ 55 (Oct, 2013).

Codeine and paracetamol may be superior to NSAIDs for moderate pain

Codeine and paracetamol may be an effective alternative to NSAIDs in patients with moderate biliary colic. A combination product of paracetamol 500 mg with codeine 30 mg, was found to provide superior pain relief to tramadol, oral or intramuscular diclofenac, ibuprofen and hyoscine in a survey of patients with biliary colic.[17] However, for the 79% of patients with severe pain it was found that NSAID analgesia was the most effective.[17]

Codeine is available fully subsidised in New Zealand in 15 mg, 30 mg and 60 mg tablets which can be prescribed in addition to paracetamol. Combination medicines containing both paracetamol, 500 mg, and codeine, 8 – 15 mg, are available in New Zealand, but only the 8 mg formulation is fully subsidised.

Opioids are an alternative to NSAIDs for severe pain

Morphine 5 – 10 mg, IM, is an alternative treatment to NSAIDs for acute pain management in patients with severe pain due to biliary colic and for patients when an NSAID is unsafe or fails to provide effective pain relief.[15] Antiemetics can be prescribed "as needed" if nausea occurs with the use of morphine (see over page).

Morphine is generally preferred over pethidine in New Zealand. Historically, morphine has been avoided in the treatment of acute biliary colic and pancreatic pain because it was thought to induce spasm in the sphincter of Oddi to a greater degree than other opioids. Pethidine has therefore traditionally been used in preference. However, a systematic review found that all narcotics increased biliary pressure to a similar degree and that there was no outcome-based evidence to support the use of pethidine over morphine.[20] Furthermore, it was concluded that morphine may be of more benefit to patients with acute pancreatitis than pethidine as it provides longer pain relief and a lower risk of seizures.[20] Pethidine is still suggested by some international guidelines for pain control in patients with acute cholecystitis while waiting for hospital admission, e.g. pethidine intramuscularly, 25 – 100 mg, which may be repeated after four hours.[15, 19]

Antispasmodic medicines may be combined with NSAIDs or opioids

Antispasmodic medicines, e.g. hyoscine butylbromide, are reported to produce effective analgesia in some patients with biliary colic, however, other patients may not gain any benefit.[8] If hyoscine butylbromide is prescribed to patients with biliary colic, it is recommended that it is used in combination with an NSAID or opioid.

Hyoscine butylbromide is available in 10 mg tablets at a recommended dose of 20 mg, four times daily.[15] Hyoscine butylbromide is also available in a 20 mg/mL injectable formulation which can be given by intramuscular or subcutaneous injection, 20 mg, repeated after 30 minutes if necessary, to a maximum of 100 mg, daily.[15]

Antiemetics may be required for some patients

Nausea is a common symptom in patients with biliary colic and may also be experienced by patients taking opioids. For some patients with biliary colic their nausea will be relieved once an analgesic has been administered. For patients that experience ongoing nausea once their pain has been controlled, antiemetics such as metoclopramide, cyclizine and ondansetron (see NZF for dosing details) may be considered. Some patients may need to trial more than one antiemetic before they achieve effective symptom control.

Surgical management of biliary colic

Patients with biliary colic should be referred for consideration of laparoscopic cholecystectomy to prevent future episodes. This surgical procedure takes approximately 60 – 90 minutes and requires an average hospital stay of one to three days.[11] Laparoscopic cholecystectomy is associated with a similar level of risk as open cholecystectomy but with less post-operative pain and faster recovery. Evidence supports early surgical intervention for patients with acute cholecystitis and the majority of these patients can be managed laparoscopically.[21] Patients with severe acute cholecystitis, whose health is too fragile to undergo surgery, can be managed through the acute episode with percutaneous drainage of the gallbladder, plus antibiotics. In all patients the individual risks and benefits of the choice of procedure will need to be balanced. Patients with severe co-morbidities may be unfit to undergo elective cholecystectomy.

Patients will be asked to consent to both laparoscopic and open procedures before surgery is performed. Conversion to open surgery generally occurs in less than 5% of patients, but is higher in patients treated acutely or in those with previous abdominal surgery. Wound complications, e.g. haemorrhage, infection and incisional hernia, bile leaks, diarrhoea and the rare but important complication of bile duct injury can occur after laparoscopic or open cholecystectomy.[11] Incomplete surgical removal of stones, injury or scarring can result in patients experiencing long-term, post-operative symptoms.

Bile duct exploration to remove common bile duct stones can be performed during laparoscopic or open cholecystectomy and is necessary if ERCP is unavailable or has failed. A Cochrane review found both surgical and endoscopic approaches to bile duct stone removal to be equally safe and effective.[22] The choice of approaches will be influenced by local availability and expertise.

The long-term consequences of gallstones and cholecystectomy

Gallstones are a risk factor for gallbladder cancer. Although 85% of people with gallbladder cancer have gallstones, only 3% of people with gallstones have gallbladder cancer.[23] The age-adjusted incidence rates of gallbladder cancer in New Zealand are reported to be 1 case per 245 000 people in males and 1 case per 135 000 people in females, which compares to an approximate incidence rate of 1 case per 2 500 people for colorectal cancer.[24, 25]

Following cholecystectomy, patients who make positive dietary changes will improve their general health, but there are no specific dietary recommendations for patients who undergo this procedure.

Gallstones and subsequent cholecystectomy are associated with a small increased risk of cancer throughout the digestive tract. In a large study of over 236 000 patients with primary cancer in the United States, gallstones were associated with

an increased risk (odds ratio) of: liver cancer (OR 2.35), small intestine carcinoid (OR 1.27), pancreatic cancer (OR 1.24) and non-cardia gastric cancer (OR 1.21).[26] In the same study cholecystectomy was associated with an increased risk of: small intestine carcinoid (OR 1.78), non-cardia gastric cancer (OR 1.26), liver cancer (OR 1.26) and pancreatic cancer (OR 1.23).[26] It has been suggested that this increased risk of malignancy is due to enhanced exposure of the stomach and small intestine to bile following cholecystectomy. This suggestion was supported by a reduced risk of colorectal cancer occurring in the colon with increasing distance from the common bile duct.[26]

ACKNOWLEDGEMENT: Thank you to **Professor John McCall,** McKenzie Chair in Clinical Science, Dunedin School of Medicine, University of Otago, Gastrointestinal and Liver Surgeon, Southern DHB and **Dr Matthew Cohen**, Senior Medical Officer and Consultant Gastroenterologist, Capital & Coast DHB for expert review of this article.

References

1. Mendez-Sanchez N, Chavez-Tapia NC, Uribe M. Pregnancy and gallbladder disease. Ann Hepatol 2006;5:227–30.
2. Chapman BA, Frampton CM, Wilson IR, et al. Gallstone prevalence in Christchurch: risk factors and clinical significance. N Z Med J 2000;113:46–8.
3. Colli A, Conte D, Valle SD, et al. Meta-analysis: nonsteroidal anti-inflammatory drugs in biliary colic. Aliment Pharmacol Ther 2012;35:1370–8.
4. Cafasso DE, Smith RR. Symptomatic cholelithiasis and functional disorders of the biliary tract. Surg Clin North Am 2014;94:233–56.
5. Bodmer M, Brauchli YB, Krähenbühl S, et al. Statin use and risk of gallstone disease followed by cholecystectomy. JAMA J Am Med Assoc 2009;302:2001–7.
6. Venneman NG, van Erpecum KJ. Gallstone disease: Primary and secondary prevention. Best Pract Res Clin Gastroenterol 2006;20:1063–73.
7. Everson G. Pregnancy and gallstones. Hepatology 1993;17:159–61.
8. Mackay S, Dillane P. Biliary pain. Aust Fam Physician 2004;33:977–81.
9. Sarin SK, Negi VS, Dewan R, et al. High familial prevalence of gallstones in the first-degree relatives of gallstone patients. Hepatol Baltim Md 1995;22:138–41.
10. Caddy GR, Tham TCK. Gallstone disease: Symptoms, diagnosis and endoscopic management of common bile duct stones. Best Pract Res Clin Gastroenterol 2006;20:1085–101.
11. National Institute for Health and Care Excellence (NICE). Single-incision laproscopic cholecystectomy. NICE, 2010. Available from: http://publications.nice.org.uk/single-incision-laparoscopic-cholecystectomy-ipg346 (Accessed Jun, 2014).
12. Salati S, Kadi A. Murphy's sign of cholecystitis– a brief revisit. J Symptoms Signs 2012;1:53–6.
13. NHS Choices. Cholecystitis, acute - complications. NHS, 2012. Available from: www.nhs.uk/Conditions/cholecystitis-acute/Pages/Complications.aspx (Accessed Jun, 2014).
14. Bencini L, Tommasi C, Manetti R, et al. Modern approach to cholecysto-choledocholithiasis. World J Gastrointest Endosc 2014;6:32–40.
15. New Zealand Formulary (NZF). NZF v23. 2014. Available from: www.nzf.org.nz (Accessed Jun, 2014).
16. Day RO, Graham GG. Non-steroidal anti-inflammatory drugs (NSAIDs). BMJ 2013;346:f3195.
17. Johnston MJ, Fitzgerald JEF, Bhangu A, et al. Outpatient management of biliary colic: A prospective observational study of prescribing habits and analgesia effectiveness. Int J Surg 2014;12(2):169-76.
18. Leitzmann MF, Stampfer MJ, Willett WC, et al. Coffee intake is associated with lower risk of symptomatic gallstone disease in women. Gastroenterology 2002;123:1823–30.
19. National Institute for Health and Care Excellence (NICE). Clinical Knowledge Summaries: Cholecystitis - acute. NICE, 2012. Available from: http://cks.nice.org.uk/cholecystitis-acute#!scenariorecommendation (Accessed Jun, 2014).
20. Thompson DR. Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therapeutic implications in treating pancreatitis. Am J Gastroenterol 2001;96:1266–72.
21. Gurusamy KS, Davidson C, Gluud C, et al. Early versus delayed laparoscopic cholecystectomy for people with acute cholecystitis. Cochrane Database Syst Rev 2013;6:CD005440.
22. Dasari BVM, Tan CJ, Gurusamy KS, et al. Surgical versus endoscopic treatment of bile duct stones. Cochrane Database Syst Rev 2013;9:CD003327.
23. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. Clin Epidemiol 2014;6:99–109.
24. Koea J, Phillips A, Lawes C, et al. Gall bladder cancer, extrahepatic bile duct cancer and ampullary carcinoma in New Zealand: Demographics, pathology and survival. A NZ J Surg 2002;72:857–61.
25. National Cancer Institute. International cancer screening network. Available from: http://appliedresearch.cancer.gov/icsn/colorectal/mortality.html (Accessed Jun, 2014).
26. Nogueira L, Freedman ND, Engels EA, et al. Gallstones, cholecystectomy, and risk of digestive system cancers. Am J Epidemiol 2014;179:731–9.