THE CLINICAL SEQUELAE OF GALLSTONES

Internal Medicine Grand Rounds
January 22, 1998

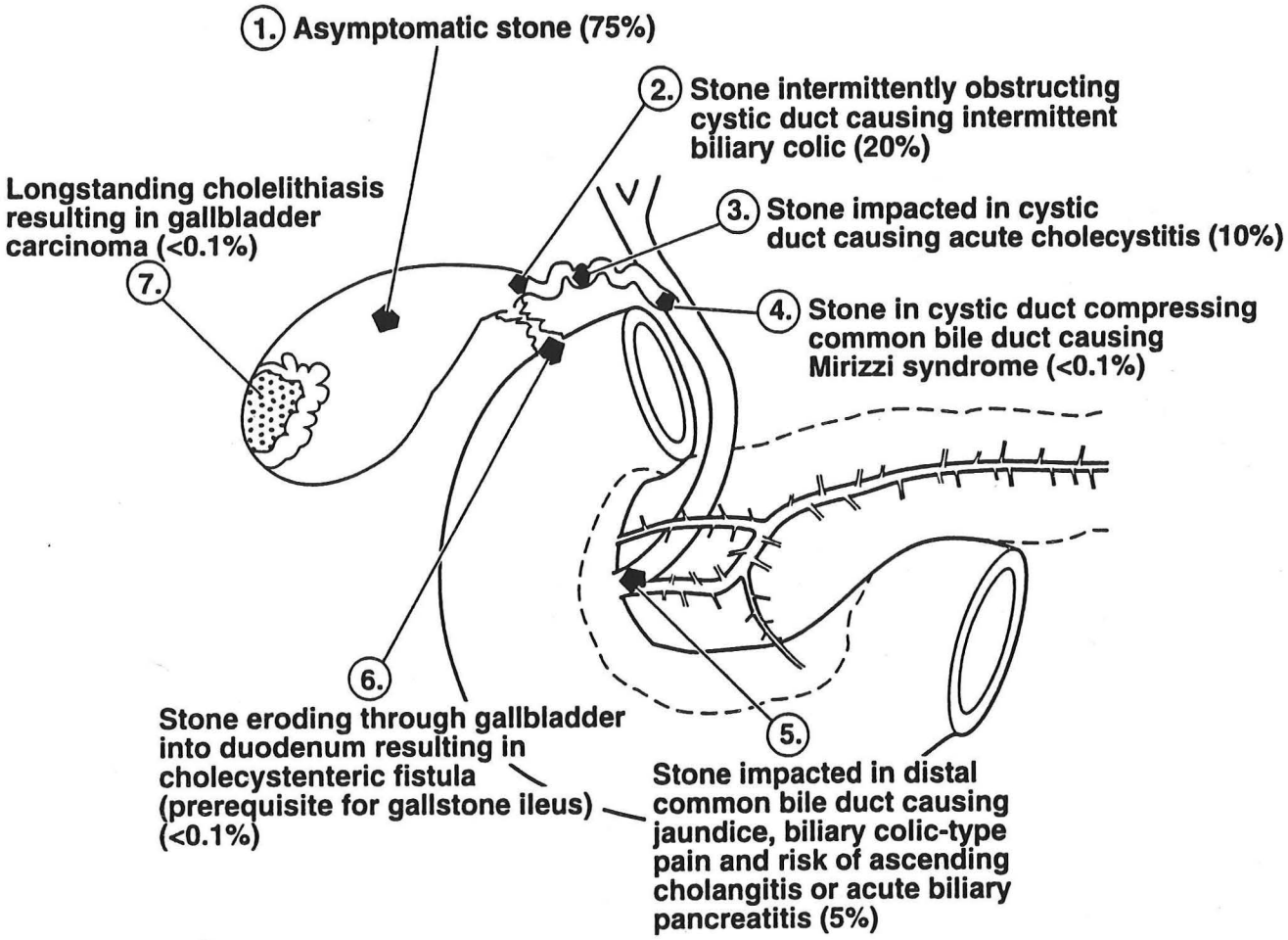

Figure 1. Schematic depiction of the complications of gallstones. The percentages approximate the frequency of that complication occurring in untreated patients, based on natural history data.

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This is to acknowledge that Lyman E. Bilhartz has disclosed no financial interests or other relationshipswith commercial concerns related directly or indirectly to this program.

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OVERVIEW

The hepatobiliary tract is a low-pressure/low-flow hydraulic excretory pathway for hydrophobic, water insoluble waste products (1). Because of the low-flow nature of the hydraulic system and the tenuous solubility of the bile constituents, bile is vulnerable to precipitation and the formation of concretions(2). Once formed, the concretions or stones only rarely spontaneously dissolve.

MORPHOLOGY AND COMPOSITION

Based largely on composition, gallstones are categorized as either cholesterol stones, black pigment stones or brown pigment stones, each category having a unique epidemiology and characteristic risk factors.

CHOLESTEROL STONES, the most common type, are composed purely of cholesterol or have cholesterol as the major chemical constituent. These stones can often be identified by inspection with the stones composed purely of cholesterol being generally large and yellow-white in appearance. Microscopically, pure cholesterol stones are composed of many long, thin cholesterol monohydrate crystals bound together by a matrix of mucin glycoproteins with a black core composed of a calcium salt of unconjugated bilirubin. Mixed cholesterol gallstones are composed of more than 50% cholesterol and are slightly more common than pure cholesterol stones. Mixed stones tend to be smaller than pure cholesterol stones and are often multiple.

BLACK PIGMENT STONES are composed of either pure calcium bilirubinate or polymer-like complexes with calcium and copper with large amounts of mucin glycoproteins. A regular crystalline structure is not present. Black gallstones are more common in patients with cirrhosis and chronic hemolytic states.

BROWN PIGMENT STONES are composed of calcium salts of unconjugated bilirubin, with varying amounts of cholesterol and protein. These stones are usually associated with infection. Bacteria present in the biliary system produce ß-glucuronidases that hydrolyze glucuronic acid from conjugated bilirubin.(3) This results in the formation of calcium salts of unconjugated bilirubin, deconjugated bile acids and saturated long-chain fatty acids.(2) Microscopically, brown stones contain cytoskeletons of bacteria, consistent with bacterial infections being a necessary antecedent of brown stone formation.

PREVALENCE AND INCIDENCE

Large studies using sonographic screening or necropsy data estimating the prevalence of gallstone disease in different populations are shown in Table 1. Although sonographic screening cannot distinguish cholesterol from pigment stones it can be assumed that 70-80% of those stones detected are cholesterol gallstones. Several interesting points can be derived from these data. There is clearly a modest difference reported in studies from different populations. These could represent real genetic and/or environmental factors or differences in the specific populations chosen for each study. In general, gallstones are 2-3 times more common in women than men and at least 10% of the population have gallstones. Most series report the prevalence for women between the ages of 20 and 55 varies from 5-20% and is 25-30% after the age of 50. The prevalence for men is approximately half that for women for a given age group. A recent study from England has suggested the prevalence of gallstone disease in that country has remained constant over a 10 year period for women over the age of 50, but has increased 8-11% in men over the age of 50 during the same period.(4)

TABLE 1. GALLSTONE PREVALENCE BY AGE IN WOMEN AND (MEN)

POPULATION	AGE				
	20-30	30-40	40-50	50-60	> 60
Mexico	11 (1)	13 (5)	20 (7)	22 (10)	27 (14)
Mexican Americans		14 (3)		26 (10)	(16)
Cuban Americans		11 (0)		19 (19)	(22)
Puerto Rico		9 (9)		21 (21)	(12)
Denmark		5 (2)	6 (2)	14 (7)	20 (13)
Sweden			17	22	
Norway	6 (5)	15 (13)	25 (18)	29 (25)	41 (37)
Italy	3 (2)	9 (3)	17 (8)	22 (12)	28 (17)
Nova Scotia	15	33	14		

Ethnic predisposition

The genetic predisposition to gallstone disease is only starting to be fully understood. Clearly, certain genetic factors play a key role in the pathogenesis of gallstone disease but these are likely to be multifactorial and to vary from population to population since many physiologic factors are also determinants of gallstone formation.

The well studied Pima Indians in southern Arizona are an example of an extremely high risk population in which 70% of the women have gallstones after the age of 25. A second high risk population are the Scandinavians in whom 50% develop gallstone disease by age 50. Other high risk populations include other Amerindian groups in Alaska, Canada, the continental United States and Bolivia and all persons living in Chile.(5)

Those with the lowest rates are from the sub-Sahara Africa(6) and Asia.(7) African-Americans have a lower prevalence than Caucasians and their rate of hospitalization for gallstone related problems is only 40% that of whites in the United States.(8)

Within a given population, first degree relatives of index cases with gallstone disease have been shown to be 4.5 times more likely to develop gallstones than matched controls(9), implying a strong genetic influence.

True incidence

The true incidence of gallstones in a given population has been much harder to elucidate. The largest study to date is of the Danish population.(10) The 5-year incidence of gallstones in men aged 30, 40, 50, and 60 years was 0.3%, 2.9%, 2.5%, and 3.3%, respectively. The corresponding rates for women were 1.4%, 3.6%, 3.1%, and 3.7%. Females clearly had higher incidence than males at 30 and 40 years of age but this difference disappeared with increasing age. These incidence figures are in accordance with estimated incidence from prevalence data reported for Denmark and other populations.(11)

RISK FACTORS

Within a population, gallstones occur sporadically but not randomly. Rather, specific risk factors have been identified that predict stone formation. Table 2 delineates these risk factors and suggests the physiologic abnormality that accounts for the increased risk.

TABLE2. RISK FACTORS ASSOCIATED WITH CHOLESTEROL GALLSTONE FORMATION	
RISK FACTOR	PROPOSED METABOLIC ABNORMALITY
AGE	Increased cholesterol secretion and decreased bile acid synthesis
FEMALE GENDER	Increased cholesterol secretion and increased intestinal transit time
OBESITY	Cholesterol hypersecretion into bile and increased cholesterol synthesis v HMG CoA reductase activity
WEIGHT LOSS	Cholesterol hypersecretion into bile, reduced bile acid synthesis and gallbladder hypomotility
TOTAL PARENTERAL NUTRITION	Gallbladder hypomotility
PREGNANCY	Increased cholesterol secretion and gallbladder hypomotility
DRUGS:	
Clofibrate	Decreased bile acid concentration as a result of suppression of 7a-hyroxylase activity and decreased Acyl-CoA: cholesterol acyltransferase (ACAT) activity
Oral contraceptives	Increased cholesterol secretion
Estrogen treatment in females	Cholesterol hypersecretion into bile and reduced bile acid synthesis
Estrogen treatment in males	Cholesterol hypersecretion into bile
Progestogens	Diminished ACAT activity and increased cholesterol secretion
Ceftriaxone	Precipitation of an insoluble calcium-ceftriaxone salt
Octreotide	Decreased gallbladder motility
GENETIC PREDISPOSITION:	
Native Americans	Increased cholesterol synthesis and reduced conversion of cholesterol into bile salts
Scandinavians	Increased cholesterol secretion into bile
DISEASES OF THE TERMINAL ILEUM	Hyposecretion of bile salts from diminished bile acid pool
LIPID PROFILE:	
Decreased HDL	Increased activity of HMG-CoA reductase
Increased Triglycerides	Increased activity of HMG-CoA reductase

Age and Gender

Since gallstones rarely dissolve spontaneously, the cumulative prevalence of gallstones not surprisingly increases with age (Table 1). In addition, cholesterol secretion into bile increases with age while bile acid formation may decrease.

Gender is the most prominent risk factor for gallstone formation with most studies reporting a 2-3 fold increase in females. The increased incidence in women is present through the fifth decade after which the male and female incidences become essentially equal(10) suggesting that estrogen may have a role in the increased cholesterol secretion into bile seen in younger women.

Obesity, Weight Loss and Total Parenteral Nutrition

OBESITY is also a well known risk factor for cholelithiasis. A large prospective study of obese women found a strong linear association between body mass index (BMI measured in kg/m^2) and the incidence of reported cholelithiasis.(12) Those with the highest BMI (>45 kg/m^2) had a sevenfold

increased risk of developing gallstones compared to non-obese controls. This same population had a yearly incidence of gallstone formation of approximately 2% per year.

Obesity is associated with increased secretion of cholesterol into the bile which may be secondary to higher levels of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity (the rate-limiting enzyme in cholesterol synthesis) which would lead to high levels of cholesterol production by the liver. No studies have been performed comparing nucleating and antinucleating factors from bile of obese and non-obese subjects.

Gallbladder motility has been studied in obese patients and no impairment in gallbladder contraction has been documented.(13) A recent case report has shown abnormal processing of the cholecystokinin receptor gene in an obese patient with gallstones.(14) Such an abnormality could lead to gallbladder stasis and thus predisposes a patient to cholelithiasis. However, this is not likely to represent a common cause of gallstone disease in non-obese or obese patients.

RAPID WEIGHT LOSS is a more recently recognized risk factor for cholesterol gallstone formation. Approximately 25% of obese patients who undergo strict dietary restriction develop gallstones and up to 50% of patients who undergo gastric bypass develop gallbladder sludge or gallstones within 6 months after surgery.(15) Up to 40% of these patients will become symptomatic from their gallstones in the same 6 month period.

The mechanisms whereby rapid weight loss causes gallstone formation are multifactorial. Many investigators have shown hepatic cholesterol secretion increases during caloric restriction.(16) Additional factors may include increased mucin production (a potent stimulator of cholesterol crystal nucleation) and decreased gallbladder motility.(17) Prevention of gallstone formation in this high risk population may be possible by administering ursodeoxycholic acid prophylactically. Shiffman and Kaplan (18) report a decreased incidence in gallstone formation from 28% to 3% in obese patients on a very-low-calorie diet if they received 600 mg of ursodeoxycholic acid daily.

TOTAL PARENTERAL NUTRITION has been associated with the development of acalculous cholecystitis as well as cholelithiasis and cholecystitis. Up to 45% of adults (19) and 43% of children (20)will develop gallstones after 3-4 months of TPN. The incidence of gallbladder sludge is even higher and can occur as early as 3 weeks after initiation of TPN.(21) The primary defect is a result of prolonged fasting which leads to gallbladder hypomotility and bile stasis. In addition, there may be a failure of the sphincter of Oddi to relax resulting in preferential flow of bile into the gallbladder. In general, patients receiving TPN have serious medical problems and are not good candidates for abdominal surgeries. Therefore, prophylactic treatment should be employed if possible. Cholecystokinin-octapeptide has been shown to be effective in preventing gallbladder sludge and gallstone formation (21) and should be used as routine prophylaxis in patients receiving long term TPN in whom no contraindication exists.

Pregnancy and Parity

Past child bearing is a frequently touted risk factor for gallstone disease. In reality, the increased risk is small (but probably significant) with increasing parity, especially in younger women(22). Pregnancy itself is a greater risk factor for the development of biliary sludge and gallstones. During pregnancy, bile becomes more lithogenic due to increased estrogen levels (23) which results in increased cholesterol secretion and supersaturated bile. In addition, gallbladder volume doubles and stasis develops (22) which also promotes sludge and stone formation.

The incidence of new sludge and stone formation during pregnancy is approximately 30% and 2%, respectively.(24) Both sludge and stones are usually silent but when biliary pain does develop it is generally associated with the presence of stones and not sludge. Women who have gallstones before they become pregnant are more likely to develop biliary pain during pregnancy than in the non-pregnant state.(24) After delivery, gallbladder motility returns to normal and the bile returns to the pre-pregnant state. Sludge disappears in 60-70% and stones in 20-30% of women following delivery.(24, 25)

Drugs

ESTROGEN is the most extensively studied drug/hormone that is associated with gallstone formation. It is hypothesized to be an important factor in cholesterol gallstone formation based on the observation that gallstones occur more frequently in females during their reproductive years. The

relationship between exogenous estrogens and gallstone formation in men is clearly established. Men taking estrogens have an increased incidence of symptomatic gallstones and of having cholecystectomies.(26) Exogenous estrogen increases biliary cholesterol secretion by 40% causing cholesterol supersaturation in the bile.(27) Estrogen therapy is also known to decrease plasma LDL-cholesterol and increase plasma HDL-cholesterol in men.(28) The decrease in plasma LDL is a result of increased hepatic LDL receptor expression which increases the clearance of plasma LDL.(29) Therefore, it is postulated the increased uptake of LDL by the liver results in an increased secretion of cholesterol into the bile.

In women, exogenous estrogen enhances lipoprotein uptake in the liver, increases cholesterol secretion into the bile, and inhibits bile acid synthesis.(30) The effects of estrogens on gallbladder motility have been mixed (30, 31) and may be a result of the particular drug formulation studied. Women taking Premarin (Averst Laboratories, New York) have at least a two-fold increased risk of developing gallstones.(32) Oral contraceptive use has also been associated with an increased incidence of gallstone formation.(33) However, more recent studies using new oral contraceptives have shown no increased risk.(34). This discrepancy is probably a result of the lower estrogen content in the newer oral contraceptives since an estrogen dose response has been previously documented.(35)

LIPID LOWERING DRUGS as a whole might be expected to alter the propensity to form gallstones since they alter key pathways in cholesterol and bile acid synthesis and metabolism. Clofibrate is a lipid lowering drug that has the greatest association with increased gallstone formation. The fibric acid derivatives have been shown to induce cholesterol supersaturation in bile and to diminish bile acid concentrations by reducing the activity of cholesterol 7α-hydroxylase (the rate-limiting enzyme in bile acid synthesis).(36) Cholestyramine and nicotinic acid have no statistical association with gallstone formation. HMG CoA-reductase inhibitors reduce the biliary cholesterol saturation index but their role in prevention or therapy of gallstone disease has not been determined.(37)

OCTREOTIDE, the somatostatin analog, has been shown to increase the incidence of gallstones in patients receiving the drug as treatment for acromegaly. The incidence of newly formed gallstones after initiation of treatment with octreotide in an Italian population was 28% (38). Decreased gallbladder motility is the recognized defect associated with octreotide administration.(39)

CEFTRIAXONE (Rocephin; Hoffmann-LaRoch, Nutley, NJ) is a third-generation cephalosporin with a long duration of action that is generally excreted in the urine. However, up to 40% of the drug is secreted unmetabolized into bile (40) reaching 100-200 times the concentration in serum and exceeding its saturation level. Once the saturation level is exceeded, ceftriaxone complexes with calcium and forms an insoluble salt.(41) Biliary sludge formation has been reported in 43% of children receiving high-dose ceftriaxone (60-100 mg/kg/day) and symptoms referable to the biliary system were reported in 19% of these patients.(42) The sludge usually spontaneously disappears after treatment is withdrawn.

Diet and Lipid Profile

High serum cholesterol does not seem to be a risk factor for developing gallstones.(43) However, hypertriglyceridemia is positively associated with an increased incidence of gallstone disease.(44) Interestingly, high density lipoprotein (HDL) cholesterol has been shown to be inversely correlated to the presence of gallstones and biliary cholesterol saturation.(45) These seemingly independent variables are actually related, since serum triglycerides tend to increase with increasing body mass and are inversely correlated with HDL levels. Therefore, those who are obese with hypertriglyceridemia and low HDL levels are at greatest risk for developing gallstones. Which factor is most important is not settled, but a recent report suggested the body mass index is not a risk factor when adjusted for serum lipids.(46)

Diet would seem to be a logical variable which could explain some of the discrepancies in gallstone prevalence reported from various countries. Unfortunately, this has not been the case. Studies to date have been conflicting especially in regard to fat consumption. The studies are too numerous to elaborate on, but even in animal models, fat consumption may or may not cause an increase in gallstone formation depending on which species is used for experimentation. Dietary cholesterol has been shown

to increase cholesterol secretion and decrease the bile salt pool but only in people in whom gallstones already exist.(47)

Systemic Disease

DIABETES is the most extensively studied systemic disease because it is believed diabetics are more prone to develop complications associated with cholelithiasis. Given hypertriglyceridemia and obesity are risk factors for developing gallstones and gallbladder motility can be impaired in diabetes, (48)it has long been felt patients with this disease are at an increased risk to develop gallstones. However, diabetes as an independent risk factor has been difficult to prove. The more recent information suggests a trend towards an increased prevalence that does not reach statistical significance.(49) If a real increased risk exists, it may be in those with hyperinsulinemia.(50)

DISEASES OF THE ILEUM are recognized risk factors for developing gallstones. Crohn's disease is the most common systemic illness affecting the terminal ileum that clearly demonstrates an increased risk.(51) The loss of specific bile acid receptors in the terminal ileum results in excessive bile salt excretion and a diminished bile acid pool that leads to lithogenic bile.

NATURAL HISTORY

The natural history of gallstones is typically defined in two separate groups of patients, those with symptomatic gallstones and those that are asymptomatic. Autopsy studies clearly show that the vast majority of gallstones are asymptomatic and remain asymptomatic. The true incidence of complications in those with asymptomatic stones (as well as symptomatic stones) is critical to providing rational, cost-effective recommendations for therapy. Unfortunately, the information available has been rather sparse and somewhat varied.

Asymptomatic Stones

The initial study that changed the course of therapy for gallstone disease was from Gracie and Ransohoff.(52) They followed 123 Michigan faculty members that had been found to have gallstones by routine screening for 15 years. At 5, 10 and 15 years of follow-up, 10%, 15% and 18% became symptomatic and none developed complications. The authors suggest the rate of developing biliary pain is about 2% per year for 5 years and then decreases over time. Only 3 patients in this study developed biliary complications and all were preceded by biliary pain. Several studies suggest the initial presenting problem in 90% of people with asymptomatic gallstones is biliary pain and not a biliary complication.(52) Thus, the incidence of complications in patients with asymptomatic stones is low and that prophylactic removal of the gallbladder for this condition is not necessary.

Subsequent studies have shown slightly higher incidence rates of biliary pain and complications(53) but only one has been a long term prospective study. The Group for Epidemiology and Prevention of Cholelithiasis (GREPCO) in Rome reported the results of 151 subjects with gallstones, 118 of which were asymptomatic upon entering the study. In those who were initially asymptomatic, the incidence of developing biliary colic, at 2, 4, and 10 years was 12%, 17% and 26%, respectively, and the cumulative biliary complication rate was 3% at ten years.(54)

Symptomatic Stones

The natural history of symptomatic gallstones follows a more aggressive course. The National Cooperative Gallstone Study showed that in those patients who had an episode of uncomplicated biliary pain in the year prior to entering the study, 38% per year had recurrent biliary pain.(55) Others have reported an incidence of recurrent biliary pain as high as 50% per year in those with symptomatic gallstones.(56) Patients with symptomatic gallstones are also more likely to develop biliary complications as a result of their gallstones. The estimated risk of developing biliary complications is estimated to be 1%-2% per year and is felt to remain relatively constant over time.(57) Therefore, cholecystectomy should be offered to patients only after significant biliary symptoms develop. Depending on the patient, a reasonable approach may also include observing the pattern of pain before

deciding upon therapy since up to 30% of patients with one episode of pain will not have a recurrent episode.

Diabetes mellitus

Diabetic patients with incidental cholelithiasis were long considered to have an increased risk of serious complications even though the gallstones were asymptomatic. More recent studies have shown the natural history of gallstones in diabetics follows the same pattern observed in non-diabetics. A prospective study of non-insulin dependent diabetics showed that after 5 years of follow-up, 15% of the asymptomatic patients developed symptoms.(58) This is roughly the same incidence reported for non-diabetics. More importantly, the complication and mortality rates were comparable to other published studies. Therefore, prophylactic cholescystectomy is generally not recommended in diabetics.

PROPHYLACTIC CHOLECYSTECTOMY

If the natural history of asymptomatic gallstones is relatively benign, even in diabetic patients, the question arises "Are there, nonetheless, patients with asymptomatic stones who would benefit from a prophylactic cholecystectomy?" We would like to be able to answer this question using evidence based medicine, but unfortunately, rigorous clinical trials addressing this issue are lacking. By resorting to anecdotal cases, inferences on the natural history of asymptomatic stones in specific subsets of patients and on cumulative clinical experience, the following *possible* exceptions to the dictum of leaving asymptomatic stones alone have been proposed: (59).

a) a young patient with sickle cell anemia and incidental cholelithiasis in whom an abdominal pain crisis would be difficult to distinguish from biliary colic or acute cholecystitis(60, 61)

b) a young woman of Amerindian ancestry with incidental cholelithiasis(62) in whom prophylactic cholecystectomy may be warranted to prevent the delayed complication of gallbladder cancer(63)

c) possibly, a patient with incidental cholelithiaisis awaiting organ transplantation(64)

d) any patient with gallbladder wall calcification (porcelain gallbladder) , who is an acceptable surgical risk, for the purpose of preventing gallbladder carcinoma as a late complication

e) a patient with incidental cholelithiasis planning prolonged space travel or other extremely remote assignments

IMAGING STUDIES OF THE BILIARY TRACT

As shown in Appendix A, a wide array of imaging technologies are available to evaluate the biliary tract(65-67). Each test has its own set of strengths and limitations and they vary widely in relative cost and risk to the patient. With the possible exception of sonography, none of the tests should be "routinely" ordered in the evaluation of the patient with suspected gallstone disease, rather, the diagnostic evaluation should proceed in a rational step-wise fashion based on the individual patient's symptoms, signs and laboratory studies(68).

Notably absent from the list of imaging studies of the biliary tract is the plain abdominal film. Though useful on occasion in evaluating patients with abdominal pain, plain abdominal films suffer from a lack of both sensitivity and specificity. Only 50% of pigment stones and 20% of cholesterol stones contain enough calcium to be visible on the plain abdominal film. Since 80% of all gallstones in the Western world are of the cholesterol type, it follows that only one-fourth stones will be detected by simple radiographs. Plain abdominal films have their greatest utility in evaluating patients with some of the unusual complications of gallstones such as emphysematous cholecystitis, cholecystenteric fistula and in detecting a porcelain gallbladder.

TABLE 3. IMAGING STUDIES OF THE BILIARY TRACT

TECHNIQUE	CONDITION TESTED FOR:	FINDINGS/COMMENTS
Sonography	Cholelithiasis	Stones present as mobile, dependent echogenic foci within the gallbladder lumen with acoustic shadowing Sludge presents as layering echogenic material without shadows Sensitivity > 95% for stones > 2 mm Specificity > 95% for stones with acoustic shadows Rarely, a stone-filled gallbladder may be contracted and hard to see with a "wall-echo-shadow" sign *Best single test for stones in the gallbladder*
	Choledocholithiasis	Stones in CBD are only seen sonographically in ≈ 50% of cases, but can be inferred by the finding of a dilated CBD (> 6mm diameter) in ≈ 75% *Sonography can confirm, but not exclude, CBD stones*
	Acute Cholecystitis	Sonographic Murphy sign (focal gallbladder tenderness under the transducer) has a positive predictive value of > 90% in detecting acute cholecystitis when stones are seen Pericholecystic fluid (in the absence of ascites) and gallbladder wall thickening to > 4 mm (in the absence of hypoalbuminemia) are nonspecific findings suggestive of acute cholecystitis
Endoscopic ultrasound (EUS)	Choledocholithiasis	Highly accurate means of excluding or confirming stones in the CBD Sensitivity of 93% and specificity of 97% Concordance of EUS with ERCP diagnosis is 95% With experienced operators, EUS can be used in lieu of ERCP for excluding CBD stones
Oral Cholecystography (OCG)	Cholelithiasis	Stones present as mobile filling defects in an opacified gallbladder Sensitivity and specificity exceed 90% when the gallbladder is opacified, but "non visualization" occurs in 25% of tests and can be due to multiple causes besides stones Opacification of the gallbladder demonstrates patency of the cystic duct, a necessary prerequisite for medical dissolution therapy or lithotripsy May be useful in the evaluation of acalculous gallbladder diseases such as cholesterolosis or adenomyomatosis (Chapter 58)
Cholescintigraphy (Hepatobiliary scintigraphy, HIDA, DICIDA scans)	Acute Cholecystitis	Assesses patency of the cystic duct- nothing more Normal scan shows radioactivity in the gallbladder, CBD and small bowel within 30-60 minutes Positive scan is defined as non visualization of the gallbladder with preserved excretion into the CBD or small bowel Sensitivity is ≈ 95% and specificity ≈ 90% with false positives seen in fasted, critically ill patients When done with CCK stimulation, gallbladder "ejection fraction" can be determined which may help in evaluating patients with acalculous biliary pain (Chapter 58) *Normal scan virtually excludes acute cholecystitis*
ERCP	Cholelithiasis	When contrast flows retrograde into the gallbladder, stones appear as filling defects and can be detected with a sensitivity of ≈ 80%, but sonography remains the mainstay of confirming cholelithiasis
	Choledocholithiasis	ERCP is the gold standard test for stones in the CBD with sensitivity and specificity of ≈ 95% Ability to extract stones (or at least drain infected bile) is lifesaving in severe cholangitis and reduces the need for CBD exploration
CT/MRI	Complications	Though not well suited for detecting uncomplicated stones, a standard CT is an excellent test for detecting complications such as abscess formation, perforation of the gallbladder or CBD, or pancreatitis Spiral CT and MR cholangiography may prove useful as a non-invasive means of excluding CBD stones

CLINICAL SEQUELAE

In essence, a gallstone can cause symptoms via only two mechanisms: It can obstruct the cystic duct or common bile duct(69) or, much more rarely, it can erode through the gallbladder wall

The clinical manifestations of these gallstones are shown schematically in Figure 1 (cover) and are summarized in more detail in Table 4 (57, 69-74).

TABLE 4. FOUR COMMON CLINICAL SEQUALAE OF GALLSTONE DISEASE

	BILIARY COLIC	ACUTE CHOLECYSTITIS	CHOLEDOCHO-LITHIASIS	CHOLANGITIS
Patho-physiology	Intermittent obstruction of the cystic duct No inflammation of the gallbladder mucosa	Impacted stone in the cystic duct Acute inflammation of the gallbladder mucosa Secondary bacterial infection in ≈ 50%	Intermittent obstruction of the common bile duct	Impacted stone in the common bile duct causing bile stasis Bacterial superinfection of stagnant bile Early bacteremia
Symptoms	Severe, poorly localized epigastric or RUQ visceral pain growing in intensity over 15 minutes and remaining constant for 1-6 hours, often with nausea Frequency of attacks varies from days to months Gas, bloating, flatulence, dyspepsia are NOT related to stones	75% are preceded by attacks of biliary colic Visceral epigastric pain gives way to moderately severe, localized pain in the RUQ, back, shoulder or rarely chest Nausea with some emesis is frequent Pain lasting >6 hours favors cholecystitis over colic	Often asymptomatic Symptoms (when present) are indistinguishable from biliary colic Predisposes to cholangitis and acute pancreatitis	Charcot's triad of pain, jaundice and fever is present in 70% Pain may be mild and transient and is often accompanied by chills Mental confusion, lethargy and delirium are suggestive of bacteremia
Physical Findings	Mild to moderate gallbladder tenderness during an attack with mild residual tenderness lasting days Often a completely normal examination	Febrile, but usually < 102 unless complicated by gangrene or perforation Right subcostal tenderness with inspiratory arrest (Murphy sign) Palpable gallbladder in 33%, especially in patients having their first attack Mild jaundice in 20%, higher frequency in elderly	Often a completely normal examination if the obstruction is intermittent Jaundice with pain suggests stones while painless jaundice and a palpable gallbladder favors malignancy	Fever in 95% RUQ tenderness in 90% Jaundice in only 80% Peritoneal signs in only 15% Hypotension and mental confusion coexist in 15% and suggest gram negative sepsis
Laboratory Findings	Usually normal In patients with findings of only uncomplicated biliary colic, an elevated bilirubin, alkaline phosphatase or amylase suggests coexisting CBD stones	Leukocytosis of 12-15,000 with bandemia is common Bilirubin may be 2-4 mg/dl and transaminase and alkaline phosphatase may be elevated even in absence of CBD stone or hepatic infection Mild amylase elevation is seen even in absence of pancreatitis If bilirubin > 4 or amylase >1,000 suspect CBD stone	Elevated bilirubin and alkaline phosphatase seen with CBD obstruction Bilirubin > 10 mg/dl suggests malignant obstruction or coexisting hemolysis Transient "spike" in transaminases or amylase suggests passage of a stone	Leukocytosis in 80% but remainder may have normal WBC count with bandemia as the only hematological finding Bilirubin > 2 mg/dl in 80% but when < 2 the diagnosis may be missed Alkaline phosphatase is usually elevated Blood cultures are usually positive, especially during chills or fever spike and grows two organisms in half of patients
Diagnostic Tests (Appendix A)	Sonography Oral Cholecystography (OCG) Meltzer-Lyon test	Sonography Hepatobiliary Scintigraphy (DICIDA, HIDA scans) Abdominal CT	ERCP Transhepatic cholangiogram (THC)	ERCP Transhepatic cholangiogram (THC)
Natural History	After initial attack, 30% have no further symptoms The remainder develop symptoms at rate of 6%/year and severe complications at 1%/year	50% resolve spontaneously in 7-10 days without surgery Left untreated, 10% are complicated by a localized perforation and 1% by a free perforation and peritonitis	Natural history is not well defined, but complications are more frequent and severe than for asymptomatic stones in the gallbladder	High mortality if unrecognized with death from septicemia Emergent decompression of the CBD (usually by ERCP) dramatically improves survival
Treatment	Elective laparoscopic cholecystectomy with intraoperative cholangiogram (IOC) ERCP for stone removal if IOC shows stones	Cholecystectomy with IOC If IOC shows stones, then CBD exploration or ERCP for stone removal	Stone removal at time of ERCP and early laparoscopic cholecystectomy	Emergency ERCP with stone removal or at least biliary decompression Antibiotics to cover gram negative organisms Interval cholecystectomy

BILIARY COLIC AND CHRONIC CHOLECYSTITIS

Biliary colic is far and away the most common presenting symptom of cholelithiasis. About 75% of patients with symptomatic gallstone disease seek medical attention because of episodic abdominal pain(71). Even in those patients who present with a complication of gallstones such as acute cholecystitis, a history of recurrent episodes of abdominal pain in the months preceding the complication can often be illicited.

Pathogenesis

The syndrome of biliary colic is caused by intermittent obstruction of the cystic duct by one or more gallstones. There is no requirement that inflammation of the gallbladder accompany the obstruction-- only that symptoms be caused by it. The term "chronic cholecystitis" should be avoided since it implies the presence of a chronic inflammatory infiltrate that may or may not be present in a given patient. Indeed, there is little correlation between the severity and frequency of colic on the one hand and the pathologic changes in the gallbladder on the other (75).

The most common histologic changes observed are mild fibrosis of the gallbladder wall with a round cell infiltration and an intact mucosa. However, recurrent episodes of biliary colic can be associated with a scared, shrunken gallbladder with Rokitansky-Aschoff sinuses (intramural diverticula). Bacteria can be cultured from gallbladder bile or gallstones themselves in about 10% of patients but bacterial infection is not thought to contribute to the symptoms.

Clinical manifestations

The pain of biliary colic is of visceral origin and as such is poorly localized(76). In a typical case, the patient experiences episodes of upper abdominal pain, usually in the epigastrium or right upper quadrant but sometimes in other abdominal locations(71). The pain may be precipitated by eating a meal, but more commonly there is no inciting event; and the pain can even begin at night. The onset of biliary colic is more frequent during periods of weight reduction and marked physical inactivity such as prolonged bed rest.

The pain of biliary colic is steady rather than intermittent as would be suggested by the word "colic". The pain gradually increases over a period of 15 minutes to an hour and then remains at a plateau for an hour or more before slowly going away. In a third of the patients, the pain has a more sudden onset and on rare occasions may abruptly cease. Pain lasting more than 6 hours suggests acute cholecystitis rather than simple biliary colic.

In order of decreasing frequency, the pain is felt maximally in the epigastrium, right upper quadrant, left upper quadrant, and various parts of the precordium or lower abdomen. It is therefore incorrect to think that pain located other than in the right upper quadrant is atypical of gallstone disease(76). Radiation of the pain to the scapula, right shoulder or lower abdomen occurs in half of patients. Diaphoresis and nausea with some vomiting is common, however, the emesis is not as protracted as in intestinal obstruction or acute pancreatitis. As with other kinds of visceral pain, the patient with biliary colic is usually restless and active during an attack(71).

Physical examination is usually normal with only mild to moderate gallbladder tenderness during an attack and perhaps mild residual tenderness lasting several days after an attack.

It should be emphasized that complaints of gas, bloating, flatulence(77), and dyspepsia, though frequently present in patients with gallstones, are probably not related to the stones themselves, rather are non-specific symptoms that are found with a similar frequency in people without gallstones. Accordingly, patients with gallstones whose only clinical manifestations are dyspepsia and other non specific upper GI tract symptoms are not appropriate candidates for cholecystectomy(71).

The natural history of biliary colic is cause for concern but not alarm. Approximately 30% of patients having an initial attack of classic biliary colic symptoms will experience no additional attacks over the next 24 months. Thus, a reasonable approach would be to offer cholecystectomy to those with recurring episodes of biliary colic(78). In the remaining 70%, the frequency of recurrent attacks varies widely from patient to patient but the pattern remains relatively similar for an individual patient over time. On an average, patients with an initial attack of biliary colic who are followed develop symptoms sufficient to warrant cholecystectomy at a rate of approximately 6% per year(78). Fortunately, the

probability of these patients developing a severe complication requiring urgent surgical intervention is only approximately 1% per year(79).

Diagnosis

In a patient with uncomplicated biliary colic, laboratory studies are usually completely normal. Elevations of bilirubin, alkaline phosphatase or amylase suggest co-existing choledocholithiasis.

SONOGRAPHY. In general, the first (and in most cases only) imaging study to be performed on patients with biliary colic is an ultrasonographic examination of the right upper quadrant. Outlined in Table 3, sonography is a rapid, non-invasive, highly sensitive and highly specific means of establishing the presence or absence of stones in the gallbladder. Despite sonography's impressive diagnostic accuracy, the sheer number of patients with suspected gallstone disease means that occasionally sonography will miss a clinically important stone and the correct diagnosis will be delayed(80). Given the relatively benign natural history of biliary colic, it is probably safe to simply follow patients for a while and move on to other diagnostic modalities in the event that symptoms recur(81).

ORAL CHOLECYSTOGRAPHY (OCG). Nowadays, OCG is generally viewed as a secondary imaging study of the gallbladder. It is reserved for patients in whom medical disolution therapy or lithotripsy of the gallstones is planned. In such cases, it is essential to establish patency of the cystic duct prior to therapy and OCG can accomplish this. On rare occasions, oral cholecystography may demonstrate a layer of small floating gallstones that were missed by sonography.

MELTZER-LYON TEST. Long before the advent of sonography and even oral cholecystography, examination of aspirated duodenal bile for the presence of cholesterol or calcium bilirubinate crystals was an established means of inferring the presence of macroscopic stones in the gallbladder. Though long since supplanted by modern imaging tests, the Meltzer-Lyon test has enjoyed a modest resurgence in popularity of late owing to the ease with which bile can be obtained at the time of an upper endoscopy or ERCP(82). The specifics of the Meltzer-Lyon test are described in more detail in Chapter 58. Briefly, gallbladder bile is aspirated from the duodenum (or common bile duct during ERCP) after stimulation of the gallbladder with an intravenous injection of CCK. The finding of either cholesterol crystals or calcium bilirubinate crystals in the bile is highly suggestive of stones in the gallbladder(83). The Meltzer-Lyon test is usually added on to another diagnostic procedure such as an upper endoscopy or ERCP as a final effort to exclude "microlithiasis" as a cause of the patient's persistent symptoms despite normal sonograms.

Differential diagnosis

The most common diseases to be considered in the differential diagnosis of a patient with recurrent, episodic upper abdominal symptoms are reflux esophagitis, peptic ulcer, pancreatitis, renal colic, lesions of the colon such as diverticulitis and carcinoma, radiculopathy and angina pectoris. Usually, a careful history will go a long way in sorting out the differential diagnosis of recurrent upper abdominal pain. For example, relief with food or antacids or antisecretory drugs suggest acid peptic disease whereas a cramping nature to the pain suggests an intestinal problem. Renal stones usually have typical findings on a urinalysis and the pain of angina pectoris is usually precipitated by exercise and does not last for hours.

The irritable bowel syndrome, like biliary colic, is common in young women but symptoms should have a distinct relationship with bowel movements (Chapter 4). Finally, shingles or a radiculopathy from osteoarthritis may produce symptoms resembling biliary colic.

Treatment

The treatment of recurrent, uncomplicated biliary colic in a patient with documented gallstones is generally an elective laparoscopic cholecystectomy(84) and is discussed in detail in Chapter 56.

ACUTE CHOLECYSTITIS

If biliary colic is the most frequent clinical manifestation of gallstone disease, then acute cholecystitis can be considered the most frequent complication of gallstone disease. Inflammation of the gallbladder wall associated with a clinical picture involving abdominal pain, right upper quadrant tenderness, fever and leukocytosis is the hallmark of acute cholecystitis. In approximately 90% of cases

of acute cholecystitis, the underlying cause is a gallstone obstructing the cystic duct (85). In the remaining 10% of cases, cholecystitis occurs in the absence of gallstones and is termed acute acalculous cholecystitis. Whereas cholecystitis due to gallstones is frequently seen in young, otherwise healthy women and has a generally favorable prognosis, acute acalculous cholecystitis is more common in critically ill elderly men and is associated with high morbidity and mortality. Acute acalculous cholecystitis is discussed in detail in Chapter 58.

Pathogenesis

Whereas biliary colic is caused by intermittent obstruction of the cystic duct by a gallstone, acute cholecystitis generally occurs when a stone becomes impacted in the cystic duct causing chronic obstruction (85). Stasis of bile within the gallbladder lumen results in damage of the gallbladder mucosa with consequent release of intracellular enzymes and activation of a cascade of inflammatory mediators.

Experimentally, if one ligates the cystic duct of an animal, the usual result is gradual absorption of the gallbladder contents without the development of inflammation(86). In animals, the installation of a luminal irritant such as concentrated bile, lysolecithin or trauma from an indwelling catheter is required to set off acute cholecystitis in an obstructed gallbladder.

Lecithin, a normal constituent of bile, is converted to lysolecithin by phospholipase A, an enzyme present in gallbladder mucosa cells. There is evidence that phospholipase A may be released by gallstone-induced mucosa trauma, followed by conversion of lecithin to lysolecithin. Although normally absent from gallbladder bile, lysolecithin is present in the gallbladder contents from patients with acute cholecystitis(87). In animal models, installation of lysolecithin into the gallbladder produces acute cholecystitis with increased protein secretion, decreased water absorption, and evidence of white blood cell invasion associated with elevated production of prostaglandin E and F_1 alpha(87). Administration of indomethacin, a cyclo-oxygenase inhibitor, has been shown to block this inflammatory response.

Studies of human tissue obtained at cholecystectomy have demonstrated enhanced prostaglandin production in the inflamed gallbladder. Additionally, intravenous indomethacin and oral ibuprofen decreased luminal pressure and the pain of acute cholecystitis in patients (88).

Supporting evidence for the role of prostaglandins in the development of acute cholecystitis comes from the prospective study in which patients presenting with biliary colic were given diclofenac, a prostaglandin synthetase inhibitor (89). Nine of forty patients receiving placebo went on to develop acute cholecystitis, whereas all of the twenty patients receiving the prostaglandin synthetase inhibitor had resolution of their episodes of biliary colic. These data suggest a chain of events in which obstruction of the cystic duct in association with one or more intraluminal factors damage the gallbladder mucosa and stimulate prostaglandin synthetase. The resulting fluid secretion and inflammatory changes promote a cycle of further mucosal damage and inflammation (89).

Enteric bacteria can be cultured from gallbladder bile in approximately half of patients with acute cholecystitis however (90)bacteria are not thought to contribute to the actual onset of acute cholecystitis. Generally, antibiotics are used in patients with suspected gallbladder perforation or gangrene or in those patients with particularly toxic presentations including fever greater than 102 degrees.

Pathology

If the gallbladder is examined in the initial few days of an attack of acute cholecystitis, distension is usually noted with an impacted stone in the cystic duct (91). On opening the gallbladder, bile, stones, inflammatory exudate and rarely pus are present. Later in the attack, the normally present bile pigments are absorbed and replaced with thin mucoid fluid, pus or blood. If the attack of acute cholecystitis is left untreated for a long period, but the cystic duct remains obstructed, the lumen may become distended with clear mucoid fluid-- so called hydrops of the gallbladder.

Histologically, changes range from mild acute inflammation with edema to necrosis and perforation of the gallbladder wall. There is surprisingly little correlation between the severity of histologic changes and the patient's symptoms (91). When the gallbladder is resected for acute cholecystitis and no stones are found, the specimen should be carefully examined histologically for evidence of vasculitis or cholesterol emboli as these systemic disorders may present with acalculous cholecystitis.

Clinical manifestations

As outlined in Table 4, three-quarters of patients with acute cholecystitis will report having had prior attacks of biliary colic (92). Often, the initial symptom that alerts the patient to the possibility that something more is afoot than a simple recurrence of biliary colic is the duration of her pain. The pain of biliary colic usually lasts more than one hour but rarely more than 6 hours. If the pain has been constant for more than 6 hours, it comes increasingly unlikely that she has uncomplicated biliary colic.

As inflammation in the gallbladder wall progresses, the poorly localized visceral pain gives way to moderately severe parietal pain that usually becomes localized to the right upper quadrant (92). Less commonly the back, or and even rarely the chest may be the site of maximal pain.

Nausea with some vomiting is characteristic of acute cholecystitis, but these symptoms almost invariably follow rather than precede the onset of pain. Emesis is not as persistent or severe as in an intestinal obstruction or acute pancreatitis.

Unlike the situation in uncomplicated biliary colic, the physical examination can, in many cases, suggest the diagnosis of acute cholecystitis. Fever is common (due to active inflammation in the gallbladder mucosa) but is usually less than 102 degrees unless gangrene or perforation of the gallbladder has occurred. Mild jaundice is present in 20% of all patients and reaches 40% in the elderly. The jaundice is often subtle with bilirubin concentrations less than 4 mg/dl (93). Bilirubin above this level suggests the possibility of common duct stones, which may be found in one-half of jaundiced patients with acute cholecystitis. Another cause of pronounced jaundice in acute cholecystitis is the Mirizzi syndrome which is discussed below (Table 5).

The abdominal exam often reveals right subcostal tenderness and a palpable gallbladder in one-third of the patients. A palpable gallbladder is more common in patients having their first attack of acute cholecystitis as repeated attacks usually result in a scared fibrotic gallbladder that is unable to distend. For unclear reasons, the gallbladder is usually palpable lateral to its normal anatomic location.

A relatively specific finding for acute cholecystitis is the Murphy sign (92). During palpation in the right subcostal region, pain and inspiratory arrest may occur when the patient takes a deep breath bringing the inflamed gallbladder into contact with the examiner's hand. As physical findings go, a positive Murphy sign in the appropriate clinical setting is a reliable predictor of acute cholecystitis though confirmation of gallstones by sonography is still warranted.

In some cases, the symptoms of acute cholecystitis are non specific with only a mild ache and anorexia; whereas others may present with toxic manifestations including fever, severe right upper quadrant pain with guarding and localized rebound tenderness.

The natural history of untreated acute cholecystitis is resolution of pain in 7 to 10 days (94). It is not uncommon for symptoms to remit within 48 hours of hospitalization. Left untreated, approximately 10% of cases will be complicated by localized perforation and 1% by free perforation and peritonitis.

Diagnosis

Perhaps because acute cholecystitis is so common, it often finds itself at the top of a list of differential diagnoses and is actually over diagnosed based on clinical criteria alone. A prospective series of 100 patients with right upper quadrant pain and tenderness and suspected acute cholecystitis revealed this diagnosis to be correct in only two-thirds of cases. The clinician must therefore use laboratory and imaging studies to confirm the presence of acute cholecystitis, exclude complications such as gangrene or perforation and to look for alternative causes of the clinical findings.

Table 4 details the most common laboratory findings in acute cholecystitis (94). Leukocytosis with a shift to immature neutrophils is common. Since common bile duct stones with cholangitis is usually part of the differential diagnoses, attention is directed to the liver function test (93). Even without any detectable bile duct obstruction, acute cholecystitis often causes mild elevations in the serum concentrations of transaminase and alkaline phosphatase. The serum bilirubin concentration may also be also mildly elevated in the 2-4 mg/dl range and even the serum amylase and lipase concentrations may be non specifically elevated. A bilirubin concentration greater than 4 mg/dl or an amylase concentration greater than 1,000 U/dl usually indicates co-existing common bile duct obstruction or acute pancreatitis and warrants further evaluation along those lines.

When the degree of leukocytosis exceeds 15,000 cells per mm^3 particularly in the setting of worsening pain, high fever (greater than 102 degrees) and chills, suppurative cholecystitis (empyema) or

perforation should be suspected and urgent surgical intervention may be required. Advanced gallbladder disease may be present even if local and systemic manifestations are unimpressive.

SONOGRAPHY is the single most useful imaging study in acutely ill patients with right upper quadrant pain and tenderness. Not only can it accurately establish the presence or absence of gallstones, but as discussed above and in Table 3 sonography becomes a highly specific extension of the physical examination. A sonographic Murphy sign is defined as focal gallbladder tenderness under the transducer and with a skillful operator and an alert patient, the positive predictive value of a sonographic Murphy sign is greater than 90% in detecting acute cholecystitis if gallstones are also present (95).

Additionally, sonography can detect non-specific findings of acute cholecystitis such as pericholecystic fluid and gallbladder wall thickening to greater than 4 mm. Both of these findings lose specificity for acute cholecystitis if ascites is present or if hypoalbuminemia (less than 3.2 g/dl) is present (95).

CHOLESCINTIGRAPHY. Since gallstones are so prevalent in the background population, many patients with non-biliary tract diseases presenting with acute abdominal pain (such as acute pancreatitis or complications of peptic ulcer disease), may have only incidental and clinically irrelevant gallstones. Cholescintigraphy's greatest utility is in these patients by its ability to exclude acute cholecystitis and allow the clinician to focus on non-biliary causes of the patients acute abdominal pain(96).

As outlined in Table 3, a normal cholescintigraphy scan shows radioactivity in the gallbladder, common bile duct and small bowel within 30-60 minutes of injection of the isotope. With only rare exceptions, a normal scintigraphy scan excludes acute cholecystitis due to gallstones as virtually all of these patients have a gallstone obstructing the cystic duct at the time of their attack. If a positive scan is defined as the absence of isotope in the gallbladder, then a "falsely negative" scan would mean that the gallbladder filled with dye in the setting of acute cholecystitis-- a situation that virtually never occurs. To be sure, a false positive scan, defined as the absence of isotope in the gallbladder in a patient who does not have acute cholecystitis does occur with regularity, especially in fasted or critically ill patients receiving total parenteral nutrition. Thus, scintigraphy should not be used as the initial imaging study in a patient with suspected cholecystitis but rather, should be used as a secondary imaging study in patients already known to harbor gallstones but in whom clinical features hold out the possibility of non-biliary causes of their acute abdominal pain (97).

In an effort to reduce the incidence of falsely positive cholescintigraphy scans, morphine augmentation is often performed if the gallbladder has failed to visualize after 60 minutes. Morphine increases pressure within the sphincter of Oddi thereby directing bile into the gallbladder unless the cystic duct is obstructed. Additional scans obtained 30 minutes after the morphine injection will occasionally cause the gallbladder to fill with isotope thereby excluding cystic duct obstruction. Unfortunately, despite use of morphine augmentation, cholescintigraphy continues to have a 60% rate of false positive results in critically ill patients.

In summary, cholescintigraphy should be thought of as a secondary imaging test aimed at establishing whether the cystic duct is obstructed or not. As such, cholescintigraphy can exclude acute cholecystitis due to gallstones but cannot confirm it (97).

ABDOMINAL CT. With respect to acute cholecystitis, abdominal CT finds its greatest utility not in merely confirming the presence of acute cholecystitis, but rather, in detecting complications such as emphysematous cholecystitis or perforation of the gallbladder and at the same time excluding other intra-abdominal pathology that may present with a similar clinical picture. For example, abdominal CT is a highly sensitive means of detecting pneumoperitoneum, acute pancreatitis, pancreatic pseudocyst, hepatic or intra-abdominal abscesses, appendicitis or obstruction or perforation of a hollow viscus. In a straight-forward case of acute cholecystitis, an abdominal CT scan is usually not warranted, however, if the diagnosis is less certain, or when the optimal timing of surgery is in doubt, the CT scan may be invaluable.

Differential diagnoses

Given the high incidence of acute cholecystitis, even a weak diagnostician will often be correct in making this diagnosis in patients with right upper quadrant pain, fever and leukocytosis. However, a surprisingly lengthy list of other conditions may present with similar clinical features. The principal conditions to consider in the differential diagnoses are appendicitis, acute pancreatitis, pyelonephritis or renal stone, peptic ulcer disease, acute hepatitis, pneumonia, hepatic abscess or tumor, and gonococcal

perihepatitis. To avoid embarrassment or worse, an astute clinician would do well to at least consider all of these possibilities prior to recommending a cholecystectomy.

Acute appendicitis is the disease most often confused with acute cholecystitis because the initial diagnostic impression is largely based on localized right abdominal tenderness, which may be lower than expected in cholecystitis or higher than expected in appendicitis. In general, fever, leukocytosis, and tenderness progress more inexorably in appendicitis. Complete abdominal sonography can usually differentiate these two entities.

Acute pancreatitis may also be difficult to distinguish from acute cholecystitis based on the history and physical examination alone. Generally, vomiting is a more prominent feature in acute pancreatitis and hyperamylasemia is more profound.

Diseases of the right kidney may produce pain and tenderness similar to that of acute cholecystitis, but the urinalysis and sonogram will usually differentiate between the two. Whereas the pain of uncomplicated peptic ulcer disease is usually chronic in nature and thus seldom confused with acute cholecystitis, a perforated ulcer may, at least initially, mimic severe acute cholecystitis. Signs of generalized peritonitis or a pneumoperitoneum strongly suggests a perforated viscus or at least the need for an emergency laparotomy.

Pneumonia with pleurisy may cause abdominal pain and tenderness but the pleuritic nature of the pain and the chest x-ray should be helpful in diagnoses.

In some instances, acute hepatitis, especially when due to alcohol, may present with rather severe right upper quadrant pain and tenderness. Fever and leukocytosis further add to the confusion with acute cholecystitis. In such cases, careful assessment of the liver function test over time along with sonography or cholescintigraphy may serve to exclude acute cholecystitis. Rarely, a liver biopsy may be warranted.

Gonococcal perihepatitis (Fitz-Hugh-Curtis syndrome) produces right upper quadrant pain, tenderness and leukocytosis, which often overshadow any pelvic complaints. Nevertheless, adnexal tenderness will be present on physical examination, and a Gram stain of the cervical smear should show gonococci.

Hepatic abscesses and tumors can usually be differentiated from acute cholecystitis on the basis of sonography findings. Prior undiagnosed gallbladder perforation may present with fever from a subhepatic abscess. Finally, Pseudolithiasis due to ceftriaxone therapy has caused symptoms resembling acute cholecystitis though the gallbladder is histologically normal.

Treatment

The patient suspected of having acute cholecystitis should be hospitalized for evaluation and treatment. Volume contraction from vomiting and poor oral intake is frequent and intravenous fluid and electrolyte repletion should be given. Oral feeding should be withheld and a nasogastric tube inserted if the patient's abdomen is distended or if there is persistent vomiting.

In straight-forward uncomplicated cases, antibiotics may be withheld. Antibiotics are warranted if the patient is particularly toxic appearing or in cases of a suspected complication such as perforation of the gallbladder or emphysematous cholecystitis. A variety of antibiotics covering Gram-negative enteric bacteria are effective. Coverage with a single agent such as cefoxitin is appropriate for mild cases while more severely ill patients should receive a broader combination such as ampicillin with an aminoglycoside or a third-generation cephalosporin and metronidazole.

Definitive therapy for acute cholecystitis is cholecystectomy(84, 98) and recent studies have demonstrated the safety and effectiveness of using a laparoscopic approach(99). Surgical management of gallstone disease and post-operative complications are discussed in the following chapter (Chapter 56).

CHOLEDOCHOLITHIASIS

Choledocholithiasis is defined as the occurrence of stones in the common bile duct. Like stones in the gallbladder, choledocholithiasis by itself may remain asymptomatic for years and clinically silent passage of stones from the bile duct into the duodenum is known to occur, perhaps frequently. Unlike stones in the gallbladder, which usually present with relatively benign bouts of recurrent biliary colic, stones in the common bile duct, when they do cause symptoms, present with life threatening complications such as cholangitis or acute pancreatitis (Chapter 48). Thus, confirmation of

choledocholithiasis generally warrants some type of intervention to remove the stones(100) whereas the incidental finding of cholelithiasis can be followed expectantly.

Etiology

Gallstones may pass from the gallbladder into the common bile duct or can form primarily in the duct. All gallstones from one patient, whether from the gallbladder or common duct, are of the same type, either cholesterol or pigment. Cholesterol stones form only in the gallbladder and thus any cholesterol stones found in the common bile duct must have migrated there from the gallbladder. Likewise, black pigment stones which are seen with old age, hemolysis, alcoholism and cirrhosis also form in the gallbladder and only rarely migrate into the common bile duct. The majority of pigment stones in the common bile duct are the softer so called "brown pigment stones" which form de novo in the common duct as a result of bacterial action on the phospholipid and bilirubin in bile(101). They are often found proximal to biliary strictures and are frequently associated with cholangitis. Brown pigment stones are associated with recurrent pyogenic cholangitis (102)(oriental cholangiohepatitis).

Fifteen percent of patients with gallbladder stones also have stones in the common duct. Conversely, of patients with ductal stones, 95% also have gallbladder stones(103). In patients who present with choledocholithiasis months or years after cholecystectomy, it may be impossible to determine whether the stones were overlooked at the earlier operation or have formed since. Obviously, if the chemical composition of the common duct stones is determined, it could be surmised that cholesterol or black pigment stones were left behind after the original operation whereas brown pigment stones presumably could have formed de novo in the interval after the cholecystectomy(103).

Stones in the common bile duct usually come to rest at the lower end of the ampulla of Vater. Obstruction of the bile duct increases bile pressure proximally and causes the ducts to dilate. Normal pressure in the duct is 10 to 15 cm water and rises to 25 to 40 cm water with complete obstruction. When pressure exceeds 15 cm water, bile flow decreases and at 30 cm water it stops.

The bile duct dilates to the point that it can be detected either sonographically or by abdominal CT in approximately 75% of cases. In patients who have had recurrent bouts of cholangitis, the bile duct may become fibrotic and thus unable to dilate. Moreover, dilation is sometimes absent in patients with choledocholithiasis because the obstruction is low grade and intermittent.

Clinical Manifestations

Little information is available on the natural history of asymptomatic common duct stones. While it is clear that in many patients such stones remain asymptomatic for months or years, the available evidence suggests that the natural history of asymptomatic common duct stones is less benign than that of asymptomatic gallstones(104).

The morbidity of choledocholithiasis stems principally from biliary obstruction, which increases biliary pressure and diminishes bile flow. The rate of onset of obstruction, it's degree, and the amount of bacterial contamination of the bile are the major factors that determine the resulting symptoms. Thus, acute obstruction usually causes biliary colic and jaundice, whereas obstruction that develops gradually over several months may present initially with pruritus or jaundice alone(104). If bacteria proliferate, life threatening cholangitis may result (discussed below).

The physical examination is usually completely normal if obstruction of the common duct is intermittent. Mild to moderate jaundice may be seen when the obstruction has been present for several days to a few weeks. Deep jaundice, particularly with a palpable gallbladder suggests a neoplastic obstruction of the common duct even when the patient has stones in the gallbladder. With long-standing obstruction, secondary biliary cirrhosis may result with physical findings of chronic liver disease.

As shown in Table 4, laboratory studies may be the only hint to the existence of choledocholithiasis(105). With bile duct obstruction, both bilirubin and alkaline phosphatase concentrations increase. Bilirubin accumulates in serum due to blocked excretion whereas alkaline phosphatase levels rise because of increased synthesis of the enzyme by the canalicular epithelium. The rise in alkaline phosphatase(106) is more rapid and precedes that of bilirubin. The absolute height of the bilirubin concentration is proportional to the degree of obstruction, but the height of the alkaline phosphatase level bares no relationship to either the degree of obstruction or its cause. In cases of choledocholithiasis, the bilirubin value typically falls in the range of 2 to 5 mg/dl (104)and rarely

surpasses 12 mg/dl. Transient "spikes" in transaminases or amylase concentrations suggest passage of a common duct stone into the duodenum.

Diagnoses

SONOGRAPHY actually visualizes common bile duct stones in only approximately 50% of cases, (107)but dilation of the common bile duct to greater than 6 mm in diameter is seen in approximately 75%. Thus, sonography can confirm or at least suggest the presence of common duct stones but cannot definitively exclude choledocholithiasis.

ENDOSCOPIC ULTRASONOGRAPHY, while clearly more invasive than a standard sonogram, has the advantage of better visualizing the CBD and, in preliminary studies, can exclude or confirm choledocholithiasis with a sensitivity and specificity of approximately 95%(108).

ERCP is the gold standard for the diagnosis of common bile duct stones(100) with a sensitivity and specificity of approximately 95%.

PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY (PTC) is also an accurate means of confirming the presence of choledocholithiasis. PTC is most readily accomplished in the setting of dilated intrahepatic bile ducts and is now used primarily when an ERCP is unavailable or was unsuccessful.

LAPAROSCOPIC ULTRASONOGRAPHY is a new imaging modality employed in the surgical suite immediately prior to mobilization of the gallbladder. Preliminary studies suggest that laparoscopic ultrasonography may be as accurate as operative cholangiography in detecting CBD stones and thereby obviate the need for the latter(109).

Differential Diagnosis

The symptoms caused by obstruction of the common bile duct cannot be distinguished from those symptoms caused by obstruction of the cystic duct. Thus, biliary colic is always part of the differential diagnosis. Of course, the presence of jaundice or abnormal liver function tests strongly points to the bile duct as the source of the problem rather than the gallbladder.

In patients presenting with jaundice, malignant obstruction of the bile duct or obstruction from choledochal cyst may be clinically indistinguishable from choledocholithiasis.

Acute congestion of the liver, associated with cardiac decompensation, may cause intense right upper quadrant pain, tenderness and even jaundice with bilirubin as high as 10 mg/dl. In this condition however the temperature is normal and the white blood cell count is normal or only slightly elevated. The patient typically has other obvious signs of cardiac decompensation. Constrictive pericarditis and cor pulmonale may also cause acute congestion of the liver with only subtle cardiac findings.

Acute viral hepatitis rarely may cause severe right upper quadrant pain with tenderness and fever. The white blood count, however, is usually not elevated while the ALT and AST are markedly elevated.

AIDS cholangiopathy(110) and papillary stenosis must be considered in HIV-positive patients with right upper quadrant pain and abnormal liver function test.

Treatment

Given the high propensity for serious complications such as cholangitis and acute pancreatitis, choledocholithiasis warrants treatment in almost all cases(111). The optimal therapy for a given patient depends on the level of symptoms, co-existing medical problems, local expertise and whether the gallbladder is intact.

Common bile duct stones discovered at the time of a laparoscopic cholecystectomy present somewhat of a dilemma for the surgeon. The operation can be converted to an open cholecystectomy with a common bile duct exploration but this approach results in greater morbidity and a more prolonged hospital stay. Alternatively, the laparoscopic cholecystectomy can be carried out as planned and the patient can return for endoscopic removal of the common duct stones by ERCP. Such an approach, if successful, cures the disease but runs the risk of needing a third procedure, namely a common bile duct exploration if the ERCP was unsuccessful at removing the common duct stones. In general, the greater the level of expertise of the therapeutic endoscopist, the more inclined the surgeon should be to simply

complete the laparoscopic cholecystectomy and have the common duct stones removed endoscopically at a later date(111).

In especially high risk patients, endoscopic removal of common duct stones may be performed without the need for cholecystectomy at all. This approach is particularly appropriate for elderly patients with other severe illnesses(112). Studies indicate that subsequent cholecystectomy for symptoms is required in only 10% of patients treated this way.

CHOLANGITIS (BACTERIAL CHOLANGITIS)

Of all the complications of gallstones, cholangitis kills most swiftly. Pus under pressure in the bile ducts leads to rapid spread of bacteria, via the liver, into the blood with resulting septicemia. Moreover, the diagnosis of cholangitis is often problematic (especially in the critical early phase of the disease) due to the absence of clinical features pointing to the biliary tract as the source of sepsis (113). Table 4 delineates the symptoms, signs and laboratory findings that can aid in an early diagnosis of cholangitis.

Etiology and pathophysiology

In approximately 85% of cases, cholangitis is caused by an impacted stone in the common bile duct causing bile stasis (113). Other causes of bile duct obstruction that may result in cholangitis include neoplasms, biliary strictures, parasitic infections and congenital abnormalities of the bile ducts. This discussion deals specifically with cholangitis caused by gallstones in the common bile duct.

Bile duct obstruction is necessary, but not sufficient, to cause cholangitis. Cholangitis is relatively common in patients with choledocholithiasis, is nearly universal in patients with post-traumatic bile duct stricture, but is seen in only 15% of patients with neoplastic obstruction. It is most likely to result when a bile duct that already contains bacteria becomes obstructed, which is the situation in most patients with choledocholithiasis and stricture but in few patients with neoplastic obstruction. Malignant obstruction, because it is more often complete than is obstruction due to stricture or common duct stones, less commonly permits the reflux of bacteria from duodenal contents into the bile ducts (113).

The bacterial species most commonly cultured are *Escherichia coli, Klebsiella, Pseudomonas*, enterococci, and *Proteus*. Anaerobic species such as *Bacteroides fragilis* or *Clostridium perfringens* are seen in about 15% of appropriately cultured bile specimens. Anaerobes usually accompany aerobes, especially *E. coli*.

The shaking chills and fever of cholangitis are due to bacteria from bile duct organisms. Regurgitation of bacteria from bile into hepatic venous blood is directly proportional to the biliary pressure and hence the degree of obstruction (113). This is the reason that decompression alone often effectively treats the illness so promptly.

Clinical manifestations

As shown in Table 4, Charcot's classic triad of pain, jaundice, and fever is the hallmark of cholangitis. Unfortunately, the full triad is only present in 70% of cases (113). The pain of cholangitis may be surprisingly mild and transient but is often accompanied by chills and rigors. Particularly in elderly patients, mental confusion, lethargy and delirium may be the only historical features obtainable.

Physical examination reveals fever to be almost universal, occurring in fully 95% of cases. Right upper quadrant tenderness occurs in approximately 90% but jaundice is clinically detectable in only 80%. Notably, peritoneal signs are found in only 15%. In severe cases, hypotension and mental confusion may co-exist indicating gram negative septicemia. Overlooked cases of severe cholangitis may present with intrahepatic abscesses as a late complication.

Laboratory studies are often very helpful in pointing to the biliary tract as the source of sepsis(114). In particular, the serum bilirubin concentration exceeds 2mg/dl in 80% of cases. It is those cases in which the bilirubin is initially normal that the diagnosis may be overlooked(105). Leukocytosis likewise is present in 80% but the white blood cell count is normal in the remainder. However, in many of those patients with normal white blood cell counts, examination of the peripheral blood smear reveals a dramatic shift to immature neutrophil forms. Alkaline phosphatase is usually elevated and the serum amylase concentration may also be elevated if pancreatitis is also present.

In the majority of cases, blood cultures are a positive for enteric organisms, especially if obtained during chills and fever spikes. The organism found in the blood is invariably the same as that in the bile.

Diagnosis

The principles of radiologic diagnosis are the same as those noted for choledocholithiasis. As shown in Appendix A, stones in the common bile duct are only seen sonographically in approximately 50% of cases (107)but can be inferred by the finding of a dilated common bile duct in approximately 75%. Due to this lack of sensitivity, a normal sonogram does not exclude the possibility of choledocholithiasis in a patient whose clinical presentation suggests cholangitis (113).

Likewise, an abdominal CT scan is an excellent means of excluding complications of gallstones such as acute pancreatitis and abscess formation, but a standard abdominal CT scan is not capable of excluding common bile duct stones. Spiral CT, as noted above, may prove useful in excluding stones in the CBD(115, 116) .

ERCP is the gold standard test for the diagnosis of common bile duct stones. Moreover, the ability of ERCP to simultaneously confirm the presence of common duct stones and establish drainage of infected bile under pressure can be life saving. If ERCP is unsuccessful, percutaneous transhepatic cholangiography (PTC) can be employed.

Treatment

In suspected cases of bacterial cholangitis, blood cultures should be obtained immediately and the patient started on antibiotics effective against the organisms listed above (113). For mild cases, it is usually sufficient to initiate therapy with a single drug, such cefoxitin, 2.0 g intravenously every 6 to 8 hours. In severe cases, more intensive therapy (e.g. gentamicin, ampicillin, and metronidazole) is indicated.

Improvement should be expected within 6 to 12 hours, and in most cases the infection will come under control within 2 to 3 days with defervescence, relief of discomfort, and falling white blood cell count. In these cases definitive therapy can be planned on an elective basis. If however after 6 to 12 hours of careful observation, the patient's clinical status declines with worsening fever, pain, mental confusion or hypotension, then the common bile duct must be decompressed emergently (113). If local expertise allows for it, ERCP with stone extraction or at least decompression of the bile duct is the treatment of choice. Controlled studies comparing ERCP with decompression of the bile duct versus emergency surgery with common bile duct exploration have shown a dramatically reduced morbidity and mortality in those patients treated endoscopically(111).

UNCOMMON COMPLICATIONS OF GALLSTONE DISEASE

Table 5 delineates the clinical manifestations, diagnosis and treatment of several uncommon complications of gallstone disease.

EMPHYSEMATOUS CHOLECYSTITIS presents with the same clinical manifestations as other cases of acute cholecystitis, but gas-forming organisms have secondarily infected the gallbladder wall and pockets of gas are evident in the area of the gallbladder fossa on sonography, plain abdominal films or an abdominal CT scan (117). Emergent antibiotics with anaerobic coverage and early cholecystectomy are warranted as the risk of perforation is high. Emphysematous cholecystitis often occurs in diabetics or older men without gallstones being present, in which case, atherosclerosis of the cystic artery with resulting ischemia may be the initiating event.

CHOLECYSTENTERIC FISTULA occurs when a stone erodes through the gallbladder wall (usually the neck) and into a hollow viscus. The most common entry point into the bowel is the duodenum followed by the hepatic flexure of the colon, stomach and jejunum. Symptoms are initially similar to those of acute cholecystitis though at times, the stone may pass into the bowel and be excreted without causing any symptoms at all(118). Because the biliary tract is decompressed, the incidence of cholangitis is not high despite gross seeding of the gallbladder and bile ducts with bacteria. Diagnosis is suspected by radiographic evidence of pneumobilia and may be confirmed by barium contrast studies of

the upper or lower gastrointestinal tract, though often the precise anatomic location of the fistula is not identified until surgery.

If the gallstone exceeds 25 mm in diameter, it may present, particularily in elderly women, with a small bowel obstruction (gallstone ileus) (119)with the ileo-cecal area being the most common site of obstruction. In such cases, a plain abdominal film may show the pathonemonic features of pneumobilia, dilated small bowel and a large gallstone in the right lower quadrant. Unfortunately, the diagnosis of a gallstone ileus is often delayed with a resulting mortality of approximately 20%.

TABLE 5. UNCOMMON COMPLICATIONS OF GALLSTONE DISEASE

COMPLICATION	PATHOGENESIS	CLINICAL MANIFESTATIONS	DIAGNOSIS/TREATMENT
Emphysematous Cholecystitis	Secondary infection of the gallbladder wall with gas-forming organisms (C welchii, E coli and anaerobic streptococci) More common in elderly, diabetic men and often occurs without stones	Similar symptoms and signs as acute cholecystitis but with a more toxic presentation	Plain abdominal series may show gas in the gallbladder fossa Sono and CT are sensitive ways of confirming gas Treatment is emergent antibiotics with anaerobic coverage and early cholecystectomy Morbidity and mortality are high
Cholecystenteric Fistula	Erosion of a (usually large) stone through the gallbladder wall into adjacent bowel, most often the duodenum followed by hepatic flexure, stomach or jejunum	Similar symptoms and signs as acute cholecystitis though sometimes the fistula may be clinically silent Lingering symptoms suggests persistence of stones in the gallbladder Stones > 25 mm, especially in elderly women, may produce a bowel obstruction or "gallstone ileus" with the terminal ileum the most frequent site of obstruction	Plain abdominal series may show gas in the biliary tree and an SBO in the case of a gallstone ileus Contrast GI series may demonstrate the fistula Fistula from solitary stones that pass may close spontaneously Cholecystectomy and bowel closure are curative Gallstone ileus requires an emergency laparotomy and the diagnosis is often delayed with a resulting mortality of ≈ 20%
Mirizzi Syndrome	Impacted stone in the gallbladder neck or cystic duct with extrinsic compression of the CBD from accompanying inflammation	Jaundice and RUQ pain	ERCP demonstrates extrinsic compression of the CBD Preoperative diagnosis is important to guide the surgical approach and minimize the risk of CBD injury
Porcelain Gallbladder	Intramural calcification of the gallbladder wall, usually in association with stones	No symptoms attributable to the calcified wall per se, but carcinoma of the gallbladder is a late complication in ≈ 20%	Plain abdominal series or CT shows intramural calcification of the gallbladder wall Prophylactic cholecystectomy is indicated to prevent carcinoma

MIRIZZI SYNDROME is a rare complication of a stone impacted in the neck of the gallbladder or the cystic duct that extrinsically compresses the common bile duct with resulting jaundice and bile duct obstruction(120, 121) . ERCP will usually demonstrate the characteristic extrinsic compression of the common duct and treatment is generally an open cholecystectomy, though endoscopic stenting and laparoscopic cholecystectomy have been successfully utilized(122). Preoperative diagnosis of Mirizzi syndrome is improtant to avoid common bile duct injury(123).

Strictly speaking, a PORCELAIN GALLBLADDER, defined as intramural calcification of the gallbladder wall is not necessarily a complication of gallstones, but is mentioned here because of the remarkable tendency of calcified gallbladders to develop carcinoma as a late complication. Diagnosis of a porcelain gallbladder can be made with a plain abdominal film or abdominal CT showing intramural calcification of the gallbladder wall. Prophylactic cholecystectomy is indicated to prevent the subsequent development of carcinoma which may occur in up to 20% of cases (124).

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