Biliary

14

Marko Bukur and Ali Salim

Introduction

As our Western population continues to age and life expectancy continues to increase, the elderly population will account for an escalating amount of health-care expenditure. As health-care providers, we must find ways to contain costs while simultaneously optimizing care of this special patient population. The most common causes of abdominal pain that requires surgical evaluation and treatment in the elderly are symptomatic biliary disease [1]. This is largely due to the fact that the incidence of cholelithiasis, particularly the symptomatic variant, increases with age [2] varying from 20 to 80 % [3, 4]. Early recognition is important due to the fact that elderly patients often present with a more complicated form of disease than their younger counterparts [5, 6]. Delays in treatment can often be precarious, leading to poor outcomes and subsequent increased use of resources. This chapter aims to review the epidemiology of biliary disease, physiologic changes associated with age progression, and the diagnostic work-up and management that will lead to optimal clinical care of elderly patients.

M. Bukur, MD, FACS
Associate Professor of Surgery, Division of Trauma, Emergency Surgery and Surgical Critical Care, Medical Director, Surgical Intensive Care Unit Bellevue Hospital Center, New York University School of Medicine, 462 First Avenue, NBV 15 S14, New York, NY 10016-9196, USA
e-mail: marko.bukur@nyumc.org

A. Salim, MD, FACS (✉)
Professor of Surgery, Division Chief Trauma, Burns and Surgical Critical Care, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA
e-mail: asalim@partners.org

Biliary Physiology and Age-Related Pathophysiologic Changes

Normal biliary secretion is an intricate, multi-step process that serves several homeostatic functions. Bile is necessary for nutrient absorption of dietary cholesterol and fats, including the soluble vitamins, as well as the mechanism for endogenous cholesterol excretion and drug and heavy metal metabolism. Bile secretion is initiated by hepatocytes into the canalicular spaces that eventually coalesce to form the complex intrahepatic biliary tree before exiting the liver as the right and left hepatic ducts. The average rate of secretion in humans is approximately 600 ml/day [7]. Bile is isoosmolar with plasma and is largely composed of water (97 %) and bile acids (2 %) with the remainder of constituents being phospholipids, cholesterol, and bile pigments [8]. Cholesterol is insoluble in water and requires a fine balance of bile acids and phospholipids to allow formation of mixed micelles that are non-lithogenic. After bile exits the liver via the hepatic ducts, they join together to form the common hepatic duct. The entrance of the cystic duct then forms the common bile duct. Communication with the cystic duct allows for bile to be stored between meals in the gallbladder. In the gallbladder, bile is concentrated through water reabsorption resulting in significantly higher concentrations of bile salts, cholesterol, and phospholipids [9]. After eating, during the gastric phase of digestion, the gallbladder normally empties 75 % of the stored bile into the duodenum prior to refilling with recycled bile acids through enterohepatic circulation.

In the elderly population, there is an age-dependent increase in the incidence of gallstones. By the age of 70 years, 15 % of men and 24 % of women have gallstones with an increase in the incidence to 24 % and 35 %, respectively, in the ninth decade of life [10]. There are three major factors that lead to the increased formation of gallstones including: altered composition of hepatic bile, increased cholesterol nucleation, and decreased gallbladder motility [11]. Several

F.A. Luchette, J.A. Yelon (eds.), *Geriatric Trauma and Critical Care*, DOI 10.1007/978-3-319-48687-1_14

age-related changes occur that lead to changes in bile salt composition. With aging, there is a corresponding decrease in bile salt synthesis [12]. This decrease can alter the fine balance in the mixed micelles that will lead to nucleation of cholesterol crystals and possible stone formation. There is also an increased incidence of bactobilia in the elderly largely due to decreased biliary duct motility. These bacteria can produce enzymes that will lead to deconjugation of bile salts and promote sludge and stone formation [11]. Finally, senescent alterations in biliary protein concentration can lead to increased bile lithogenicity.

Changes in cholesterol metabolism are also responsible for stone formation in the elderly. There is an increased relative amount of cholesterol present in the bile of older patients. This leads to nucleation of cholesterol crystal as they become insoluble in the aqueous bile and serve as a nidus for salt precipitation and subsequent stone formation [11]. Additionally, there are multiple factors that lead to altered gallbladder motility as age increases such as decreased physical activity, decreased responsiveness to cholecystokinin, and the presence of comorbidities such as diabetes mellitus [11–13]. Taken together, all of these age-related pathophysiologic changes lead to an increased propensity for gallstone formation and their subsequent pathologic sequelae.

Perioperative Considerations

The expected mortality for elective cholecystectomy in the general population is less than 0.1 %; however this risk rises in the elderly population particularly in the presence of coexisting comorbidities, decreased physiologic reserve, and delays in therapy resulting in emergent operative intervention. In elderly patients that undergo appropriate perioperative evaluation and elective operation have outcomes that are similar to younger patients. In a recent population-based study utilizing a national Medicare database, Fry et al. [14] examined the 90-day outcomes in patients over 65 years of age undergoing elective laparoscopic cholecystectomy. They found that the in-hospital mortality in this patient cohort was 0.7 % with another 1.3 % of patients expiring in the 90-day interval post discharge. Therefore, elderly patients should be appropriately risk stratified in conjunction with the patient's primary physician and anesthesiologist. Recently, a helpful nomogram created by examining Medicare claims data was published by Parmar [15] and colleagues that may aid in identifying elderly patients with symptomatic cholelithiasis that are at the greatest risk for ongoing biliary complications. The nomogram known as the PREOP-Gallstones (Predicting Risks of Complications in Older Patients with Gallstones) model takes into account several demographic factors, preexisting comorbidities, and etiology of gallstone complications to identify two patient cohorts: one that has a "low risk" of subsequent biliary-related complications (<10 % over 2 years) and the other "high-risk" group with a >40 % risk of recurrent symptoms. Though this nomogram was created from a retrospective database, it may provide an individualized assessment of risk in patients presenting with symptomatic biliary disease that allows for an objective discussion between the patient and surgeon regarding the risks and benefits of operative intervention. Further prospective studies examining the PREOP algorithm need to be undertaken.

Major risk factors for cardiopulmonary-related morbidity can be quickly assessed with minimal ancillary testing by assessing the patient's pre-illness level of activity through METs or metabolic equivalents [16], ASA score [17], or Goldman cardiac risk profile [18]. For those patients that require more intensive cardiac evaluation, well-established guidelines are available [16].

Careful perioperative management can reduce the risk for major postoperative complications and can often be accomplished through simple interventions. A detailed review of the patient's pre-illness medications should be carried out and assessed for polypharmacy or drug interactions. It is also important to take note of pre-existing cardiac medication, particularly beta-blockers as withdrawal of these medications has been tied to adverse cardiac outcomes [19, 20]. Intraoperative maintenance of normothermia is important as the elderly have impaired thermoregulation [21], and hypothermia has been linked to an increased incidence of adverse cardiac events [22] and wound complications [23].

Elderly patients are also at increased risk for early postoperative delirium that leads to increased morbidity, prolonged hospital stays, and delayed recovery of functional status [17]. Early recognition is important to halt progression. A vigilant search for common inciting factors such as sepsis, electrolyte disorders, or adverse medications should be undertaken. It is also important to note that inadequate analgesia can exacerbate delirium and lead to increased cardiopulmonary complications [17]. Judicious use of a multimodal analgesic approach can lead to enhanced recovery and decreased morbidity [24] and should be an integral part of the perioperative plan.

Diagnostic Investigation

As previously stated, biliary diseases are the most common cause of surgical pathology in the elderly population [25]. However, unlike their younger counterparts, the clinical presentation is often more subtle. Failure to identify and treat surgical conditions can lead to increased mortality even in patients that are admitted to the hospital for observation [5]. There are several physiologic reasons that are responsible

for the diagnostic challenge in the elderly. Decreased immune function is seen with increasing age [26] which can alter the typical inflammatory response seen with acute intra-abdominal processes [5, 27]. This leads to impaired ability to fight infection and altered pain perception [26] which often delays clinical presentation. The presence of medications or comorbid conditions can also alter physical exam findings. Nonsteroidal anti-inflammatory drugs can mask fever, and steroids can alter the leukocyte count and immune response, while patients that present with "normal" blood pressure and a history of hypertension may have significant occult hypoperfusion. Additionally, it is important to note that the presence of beta-blockers may blunt the tachycardic response seen with serious intra-abdominal pathology. The above pitfalls should all be carefully taken into account when evaluating elderly patients with suspected biliary disease as these patients can present with frank gallbladder perforation, gangrene, emphysematous cholecystitis, or ascending cholangitis with minimal symptomatology [28]. There should be a low threshold for ordering ancillary lab work and imaging investigations.

Laboratory Testing

The most commonly ordered laboratory tests used in the evaluation of biliary disease are complete blood count (CBC), metabolic panel, aminotransferases, alkaline phosphatase, bilirubin, and coagulation panel. Each of these can provide clinically useful information but should not be relied upon exclusively to eliminate pathology.

Often the most scrutinized value on the CBC is the white blood cell count. It can be helpful when elevated but should be noted that unlike in younger patients can be normal in 30-40 % of patients with acute gallbladder pathology [26]. The hemoglobin and hematocrit should also be carefully examined, as microcytic anemia can be indicative of a possible occult malignancy. The metabolic panel should be reviewed as the elderly patient often has electrolyte abnormalities that will need to be addressed prior to operative intervention. This is especially true when the patient is on antihypertensive medications such as diuretics, beta-blockers, ACE inhibitors or angiotensin receptor blockers, and digitalis as these are all well known to cause metabolic abnormalities.

The liver function panel may also be helpful in establishing a working diagnosis prior to diagnostic imaging. Aminotransferase elevations are indicative of liver injury. There may be modest elevations (<500 IU/L) seen with acute/chronic cholecystitis, but the absence of elevation should not exclude this diagnosis as a significant proportion of elderly patients can have normal liver function tests [26]. Markedly elevated aminotransferase levels (>500 IU/L) are seen with acute biliary obstruction such as in choledocholithiasis or biliary pancreatitis.

Markers of cholestasis include serum bilirubin and alkaline phosphatase. Measuring fractionated bilirubin is helpful because it allows discrimination of the predominant source of bilirubin elevation (i.e., conjugated vs. unconjugated). Normally the total bilirubin is predominantly unconjugated and less than 1.2 mg/dl. Elevations in the conjugated form of bilirubin are indicative of biliary tract obstruction, particularly when combined with an elevation in alkaline phosphatase. Total bilirubin levels have also been shown to be predictive of benign versus malignant obstruction depending on the level of elevation [29] and may assist in performing the appropriate diagnostic work-up. Isolated elevation of the alkaline phosphatase level should also not be ignored as it can be elevated with partial or incomplete biliary obstruction.

It is important to also take note of the coagulation panel in elderly patients presenting with suspected biliary disease. Biliary obstruction can cause elevation in the PT/INR due to malabsorption of vitamin K. This fat-soluble vitamin requires bile to aid in its digestion and absorption in the terminal ileum. Malnutrition is also common in the elderly and can also lead to coagulation derangements [30]. Marked elevation in these parameters is indicative of severe hepatocellular dysfunction or chronic long-standing disease with progression to liver failure.

Noninvasive Imaging

Plain Radiographs

Often one of the earliest tests ordered during the evaluation of acute abdominal pain are an upright chest x-ray and flat plate of the abdomen. Though these are often ordered by the emergency department prior to surgical consultation, they should not be neglected if available. In the Western hemisphere, cholesterol is the main component present in gallstones (>75 %) with the remainder being composed of calcium bilirubinate [31]. Because of the lack of calcification, only 15–20 % of stones will be visualized on plain films [32]. Though the sensitivity for stones is clearly not acceptable for diagnosis, there are other features that should be sought. The presence of pneumobilia in a patient that has not been instrumented is indicative of not only gallstones but also biliary-enteric fistula. When pneumobilia is combined with evidence of small bowel obstruction (see Fig. 14.1) on plain films in a patient that has never had abdominal surgery, this is virtually diagnostic of gallstone ileus. Lastly, although a rare entity (0.06–0.8 %), complete calcification of the gallbladder wall ("porcelain gallbladder") may also be seen on plain radiography [33].

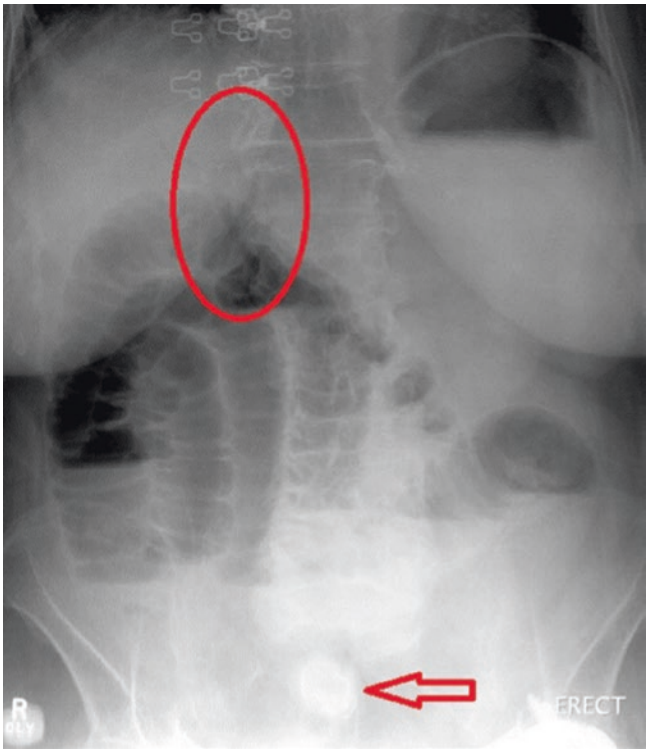

Fig. 14.1 Plain abdominal radiograph of a patient with gallstone ileus. Note the presence of pneumobilia depicted in the circled area. Gallstones may not be present due to lack of calcium composition

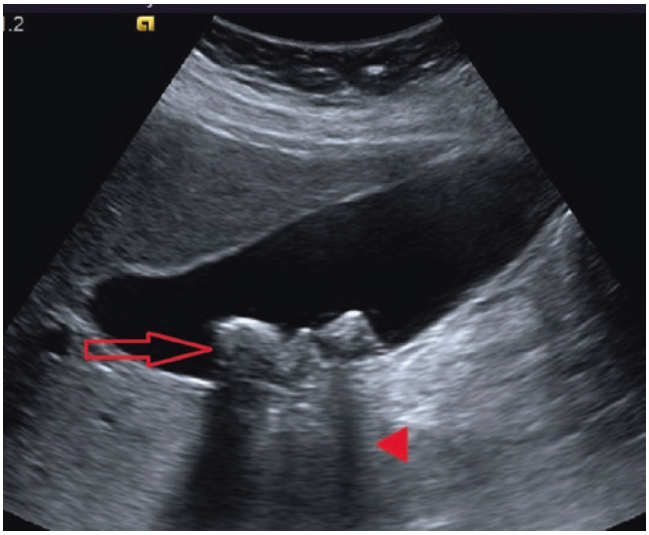

Fig. 14.2 Abdominal ultrasound documenting cholelithiasis. Note the hyperechoic stones (*arrow*) and posterior acoustic shadowing (*arrowhead*)

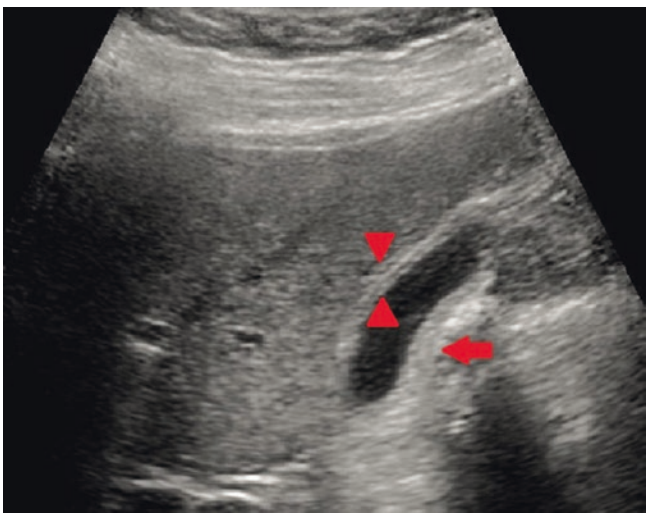

Fig. 14.3 Ultrasound depicting the findings of acute cholecystitis. Note the presence of gallbladder wall thickening (*double arrowhead*) and pericholecystic fluid (*single arrow*)

Ultrasound

Ultrasound has become the initial diagnostic test of choice in patients with suspected biliary disease. The test can be rapidly performed at the patient's bedside and does not require the use of radiation. Ultrasound is highly accurate for identifying stones that are ≥5 mm in size (>96 %) [32]. In order to detect stones, they must be echogenic, have posterior acoustic shadowing, and be mobile (see Fig. 14.2). False-negative results may be seen with decreased sonographer experience, large amounts of bowel gas, small stone size (<3 mm), or with soft pigmented stones ("brown stones") [32–34]. Examining the gallbladder with the patient in multiple different scanning positions can lower the rate of false negative exams.

Ultrasonography is also helpful in establishing the diagnosis of acute and chronic cholecystitis. In the setting of acute cholecystitis, the most reliable finding is a sonographic Murphy's sign or tenderness over the gallbladder with transducer pressure. This finding is 87 % specific for the diagnosis of acute cholecystitis and has a positive predictive value of 92 % when stones are also visualized [35]. False-negative sonographic Murphy's sign may occur in patients that are immunosuppressed, obtunded, recently medicated, or have denervated gallbladders (i.e., diabetics or gangrene of the gallbladder) [32]. Other findings that are indicative of acute cholecystitis include gallbladder wall thickening (>3 mm), which is present in 50 % of cases, as well as the presence of pericholecystic fluid (see Fig. 14.3) [32, 35]. It should be noted, however, that these findings are nonspecific and may occur with adjacent right upper quadrant pathology. The ultrasonographic diagnosis of chronic cholecystitis can also be suggested by nonspecific gallbladder wall thickening due to fibrosis with resultant contraction and near obliteration of the gallbladder lumen producing the "double arc" sign [36].

It should also be noted that right upper quadrant ultrasound is also the initial imaging study of choice to screen for choledocholithiasis. It allows for quick assessment of the bile duct size and continuity. The extrahepatic common bile duct should be measured at the level of the right hepatic artery and

not exceed 6 mm, while the intrahepatic bile ducts should not exceed 2 mm in size [34]. With adequate sonographer experience, the level of biliary obstruction can be identified in 92 % of patients, and overall sensitivity for choledocholithiasis can reach 75 % [34]. It is important to emphasize that choledocholithiasis can also be present in the absence of biliary ductal dilation in 25–33 % of cases [37]. When this occurs or when stones are less than 5 mm in diameter combined with overshadowing by bowel gas, the sensitivity of ultrasound drops considerably. Endoscopic ultrasonography has considerably better sensitivity at detecting choledocholithiasis (96 %) and should be considered in select cases of presumptive biliary obstruction (i.e., low or intermediate probability of retained common duct stones) [38]. Endoscopic ultrasound has been shown to have equivalent sensitivity and specificity to endoscopic retrograde cholangiopancreatography (ERCP) and avoids not only radiation exposure but also potential complications (i.e., bleeding, perforation, and pancreatitis). In a large review of patients undergoing both endoscopic ultrasound and ERCP, Petrov and Savides [39] found that 67 % of patients could be spared ERCP with a negative ultrasound examination without any documented recurrence of common bile duct stones. Additionally, the safety of endoscopic ultrasound in elderly patients with comorbidities was demonstrated in a group of 1000 patients, which revealed that there were no age-related differences in procedure-related complications [40].

Biliary Scintigraphy (HIDA)

Biliary scintigraphy involves the administration of radiolabeled technetium iminodiacetic acid, which is taken up by the hepatic parenchyma and excreted into the bile with eventual flow into the gallbladder. The use of HIDA has largely declined into a second-line test for calculous biliary disease due to its increased expense, amount of time needed to complete the study, and the use of ionizing radiation. HIDA is considered positive for acute cholecystitis when there is the absence of gallbladder visualization within 60 min (see Fig. 14.4). This test can be carried out in a delayed fashion for up to 4 h; nonvisualization during this extended time frame is considered consistent with chronic cholecystitis [41]. Scintigraphy has excellent diagnostic sensitivity (>95 %), particularly in nonhospitalized patients that are much less likely to have false-positive imaging studies [41]. False-positive studies may be seen in up to 30–40 % of patients that are hospitalized for a reason other than abdominal pain, which is a common scenario in the elderly population [42]. Reasons for false-positive exams include: prolonged fasting, cholestasis secondary to hepatic disease, or prolonged parenteral nutrition [32]. HIDA can also play a role in diagnosing postoperative biliary complications (i.e., diagnosing postoperative bile leak) as well as in those patients with suspected biliary motility disorders such as biliary dyskinesia. However, due to the previously mentioned limitations, differences in cost and radiation exposure ultrasonography should be considered as the initial diagnostic imaging test of choice for most biliary diseases.

Computerized Tomography

Computerized tomography (CT) has variable sensitivity in detecting gallstones secondary to the variable amount of calcification present and thus is also a second-line imaging study in the work-up of biliary disease. Those stones that are predominantly composed of cholesterol (>60 %) will be more difficult to identify due to their similar radiographic density as the surrounding bile. CT has lower sensitivity as compared to ultrasonography in identifying choledocholithiasis (75–80 %) (see Fig. 14.5) [32, 43] but can provide

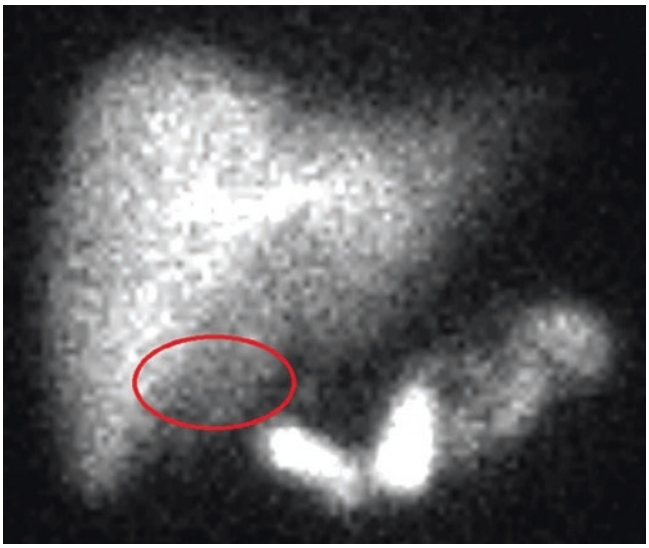

Fig. 14.4 Example of a positive HIDA scan. Note the absence of radioactivity in the area of the gallbladder fossa (*highlighted oval*)

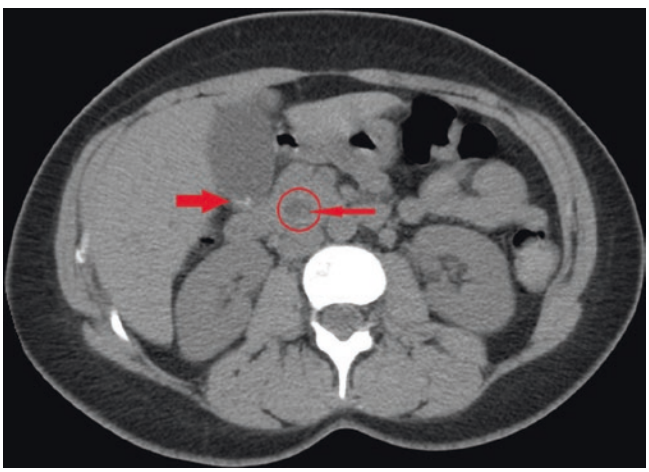

Fig. 14.5 CAT scan of the abdomen showing a stone (*thin arrow*) in a dilated common bile duct (*circled*) along with cholelithiasis (*thick arrow*)

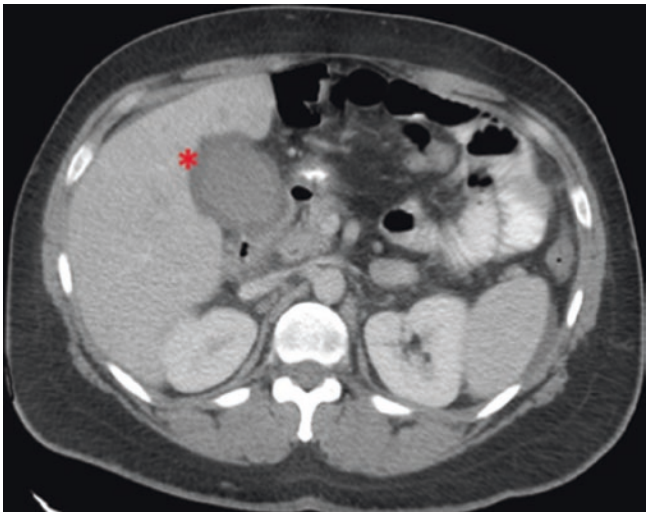

Fig. 14.6 CAT scan of the abdomen showing evidence of acute cholecystitis. Notice distention of the gallbladder (*asterisk*) with surrounding pericholecystic fluid

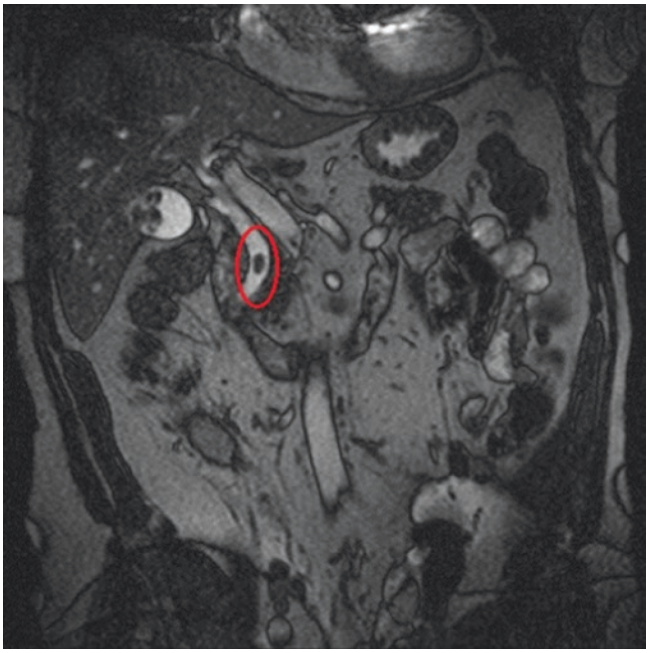

Fig. 14.7 T2-weighted MRCP showing a large stone in the common bile duct (*highlighted oval*)

information regarding ductal anatomy. CT imaging is most useful in demonstrating gallbladder size, wall thickness, and surrounding inflammatory changes associated with acute cholecystitis making it highly specific (99 %) for this particular diagnosis (see Fig. 14.6) [44]. In the setting of suspected malignancy, CT is the diagnostic image of choice because it allows assessment of not only the gallbladder but also surrounding structures such as the liver, porta hepatis, identification of lymphadenopathy, or pancreaticoduodenal pathology [45]. In the elderly patient with pre-existing renal disease, diabetes, or certain medications (i.e., ACE inhibitors, NSAIDs, or metformin), caution should be taken with the administration of intravenous contrast as this can precipitate or worsen renal failure. Gentle intravenous fluid administration, sodium bicarbonate, and/or Mucomyst prophylaxis should be considered in these patients as well as ensuring that iso-osmolar contrast is administered [46]. Because of the increased cost and associated radiation exposure, CT scanning should only be considered when there is diagnostic uncertainty and other abdominal pathology is suspected [47].

Magnetic Resonance Imaging and Cholangiopancreatography (MRI/MRCP)

MRI, though not frequently used as an initial imaging test, has excellent ability to identify gallstones due to the sharp contrast in signal intensity between bile and stones on T2-weighted images [48]. This excellent resolution of stones which are as small as 2 mm in size has made MRCP the diagnostic test of choice for identifying choledocholithiasis (see Fig. 14.7) in asymptomatic patients with moderate to high probability based upon clinical examination and laboratory studies. MRCP has excellent sensitivity (81–100 %) and specificity (85–99 %) for choledocholithiasis and is comparable to ERCP in diagnostic accuracy without the invasive risk [49]. MRCP becomes less sensitive in studies with microlithiasis, pneumobilia, motion artifact, or stones in the peri-ampullary region [50]. MRI can also be useful in those with malignant disease as it images the gallbladder wall, liver parenchyma, and biliary tree with high resolution. MRI may be difficult to obtain in elderly patients with dementia or claustrophobia due to the tight confines of the imaging magnet. Also those with pacemaker or defibrillator devices may also not be candidates for MRI, though certain devices have been prospectively observed after imaging without any adverse effects [51].

Invasive Imaging

Endoscopic Retrograde Cholangiopancreatography

Advancements in endoscopy techniques and increased experience have made ERCP widely available, and it remains the gold standard for the diagnosis of the majority of biliary pathology. However, due to its invasive nature and improvements in the aforementioned noninvasive imaging techniques, ERCP has largely become a planned therapeutic procedure. Those patients presenting with symptomatic choledocholithiasis (i.e., pain, jaundice, fever) or with documented common duct stones on imaging are clearly potential candidates for ERCP (see Fig. 14.8). Predicting which asymptomatic patients will ultimately require ERCP is more difficult, but advanced age (>55 years), hyperbilirubinemia

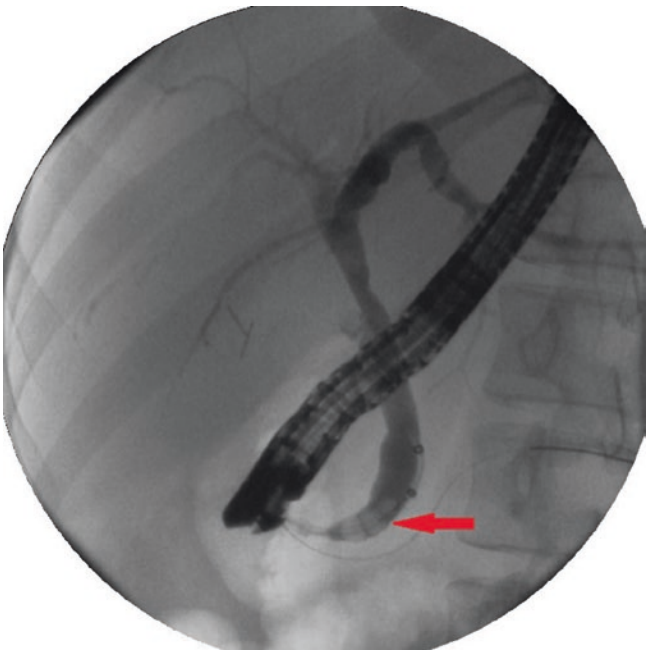

Fig. 14.8 An ERCP demonstrating a dilated common bile duct with multiple stones (*arrow*)

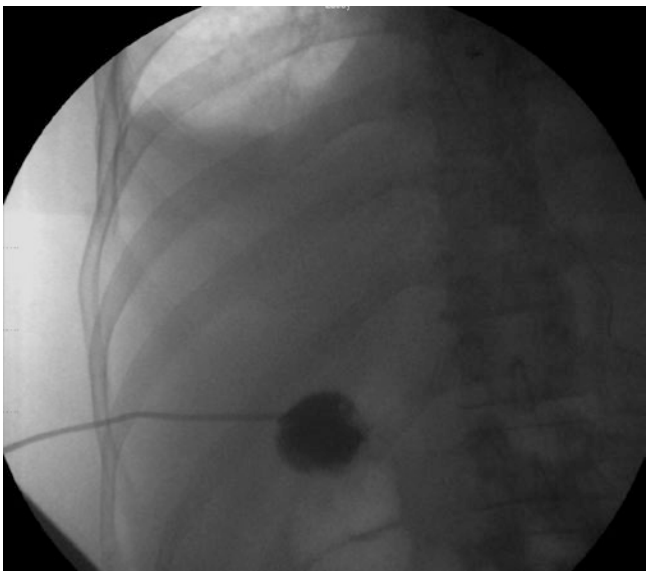

Fig. 14.9 PTC done under fluoroscopy for acute cholecystitis

(>1.8 mg/dl), and common duct dilation have all been shown to increase the likelihood of a therapeutic ERCP [52]. As previously mentioned, endoscopic ultrasound prior to ERCP may eliminate a number of nontherapeutic studies. The success rate for ERCP for common bile duct procedures is near 98 % in experienced hands [53]. ERCP is associated with a number of well-described complications, with the most common being post ERCP pancreatitis, with a reported incidence ranging from 5 to 10 %. Despite the possibility of post ERCP complications, elderly patients appear to tolerate the procedure as well as their younger counterparts [54].

Percutaneous Transhepatic Cholangiography (PTC)

PTC involves the percutaneous passage of a needle into the liver parenchyma under fluoroscopic or ultrasound guidance and then either into the gallbladder or biliary tree for diagnostic and/or therapeutic purposes (Fig. 14.9). This technique was initially introduced in 1979 and remains a valuable option for treating biliary pathology when ERCP is either unavailable or unsuccessful, particularly in the critically ill population [55, 56]. This less invasive technique can be used to successfully treat cholangitis or surgery-related biliary complications in elderly critically ill patients with a high success rate (>95 % [57]). Alternatively, the gallbladder can be cannulated to allow decompression for high-risk patients presenting with acute cholecystitis which is known as a percutaneous cholecystostomy tube. It should be noted that PTC carries a greater complication risk than ERCP because the catheter is passed through the liver into the biliary tree. This procedure can result in post-procedure hemorrhage, septic shock from bacterial translocation, or bile peritonitis.

Benign Calculous Diseases

Acute Calculous Cholecystitis

Clinical Presentation and Diagnosis

In the overwhelming majority of patients with acute cholecystitis, there is cystic duct obstruction by an impacted acalculous. This classically causes severe, persistent epigastric and right upper quadrant pain (especially with a positive Murphy's sign) that may radiate to the patient's back and be associated with nausea or vomiting. In most cases, the patient will recall more "minor" previous episodes that are in fact biliary colic, but acute cholecystitis can be the initial presentation of symptomatic gallstone disease in 15–20 % of patients [58]. In addition to the abdominal findings, there are also typically signs of systemic inflammation such as fever, tachycardia, and leukocytosis. In addition to leukocytosis, other laboratory tests that may be abnormal include: elevation of C-reactive protein and mild elevation of serum bilirubin and transaminases (<500 IU/L). Worse outcomes have been demonstrated in elderly patients presenting with LFT elevation in the setting of acute cholecystitis [59]. If the serum bilirubin is greater than 2 mg/dL, particularly the conjugated form, or serum transaminases are > 500 IU/L, choledocholithiasis should be suspected as the incidence of coexisting common bile duct stones in the elderly is high (10–20 %) [53]. It is important to emphasize, however, that the "classic" presentation in the elderly patient is often the exception rather than the rule as a significant percentage will

have no fever, abdominal pain, nausea/vomiting, or normal laboratory investigation [5, 60, 61]. In the debilitated noncommunicative patient, the only presenting symptoms of acute cholecystitis will be a change in mental status or poor oral intake [61, 62].

When the diagnosis of acute cholecystitis is suspected, abdominal ultrasonography is the initial imaging test of choice. A sonographic Murphy's sign combined with the presence of stones, gallbladder wall thickening, and pericholecystic fluid essential clinch the diagnosis. In cases where the diagnosis is less clear, or when there are no stones visualized, a HIDA scan may be useful. The CT findings of acute cholecystitis or potential gallbladder malignancy could also be assessed in patients that have this imaging test ordered for abdominal pain of unknown etiology.

Treatment of Acute Calculous Cholecystitis

Ongoing cystic duct obstruction causes inflammation and can lead to bacterial infection in the bile as well as ischemia of the gallbladder wall. Initial supportive measures such as bowel rest, intravenous fluid hydration, and analgesics are appropriate. The Infectious Diseases Society of America guidelines recommend empiric antimicrobial therapy in cases of clinically suspected infection [63]. Initial therapy should include coverage against microorganisms in the *Enterobacteriaceae* family. Appropriate initial antibiotic choices for noncomplicated cases include second- or third-generation cephalosporins or a combination of fluoroquinolones combined with metronidazole [63]. For patients presenting with severe sepsis or those that are considered high risk (i.e., elderly, diabetics, or the immunocompromised), broad-spectrum antibiotics such as piperacillin/tazobactam or aminoglycosides should be used [63].

The timing and choice of surgical intervention for acute cholecystitis has undergone considerable debate and change over the past several decades. Laparoscopic cholecystectomy has become the initial operative intervention of choice due to its superior outcomes compared with open surgery [64, 65]. The techniques of laparoscopic cholecystectomy are beyond the scope of this chapter and can be found elsewhere [66]. The traditional treatment approach involved initial nonoperative management with supportive measures and antibiotics in the acute inflammatory period followed by delayed surgical cholecystectomy. The perceived advantage of this approach was that the operation would be technically easier due to lack of acute inflammation. Besides the additional cost incurred with this approach, the recurrence rate of acute cholecystitis can be as high as 30 % over a 3-month waiting period [67–69]. It is important to note that in one third of these recurrences, patients presented with biliary obstruction (i.e., cholangitis and biliary pancreatitis that were more severe than the initial presentation) [67]. Elderly patients are also known to be more likely to present with complicated acute cholecystitis (i.e., gangrene, perforation, or emphysematous cholecystitis), all of which are more likely to require emergent surgical intervention with subsequently increased morbidity and mortality [26, 70].

Two recent systematic reviews of the literature compared early laparoscopic cholecystectomy (within 24–72 h) versus late operation (6–12 weeks after initial presentation) [71, 72]. Both meta-analyses found that there were no significant differences in conversion rates to open procedures, incidence of common bile duct injuries, or postoperative complications. Early laparoscopic cholecystectomy was also shown to be associated with decreased hospital lengths of stay as well as total costs [71]. However, it should be noted that in one of the meta-analysis, the incidence of bile leaks was higher in the early cholecystectomy group (3 % vs. 0 %) [71]. Also due to the small number of total patient in these pooled randomized trials (n = 451), the incidence of common duct injury could easily be over- or underrepresented in either group due to the low overall incidence of this complication (0.4–0.6 %) [73]. Despite these limitations, the consensus of both meta-analyses is that early laparoscopic surgery is safe in the hands of experienced surgeons and should be considered the preferred management strategy in patients with acute cholecystitis.

Even with these evidence-based recommendations, elderly patients have been shown to be more likely to be managed differently than younger patients. Previous studies have documented that up to 30 % of elderly patients do not have any therapeutic intervention for acute gallstone disease [74, 75]. These delays in treatment are also well documented to result in another symptomatic biliary admission (i.e., cholecystitis, cholangitis, or biliary pancreatitis) in up to 38 % of patients [76, 77]. This finding was perceived to be secondary to increased comorbidities or presentation with acute complicated disease [6, 75]. Recently, in a single-institution review, Bergman and colleagues showed that this might not be the case [70]. They found that increasing age was independently associated with a lower likelihood of surgical intervention after adjusting for severity of biliary disease as well as pre-existing medical comorbidities. Additionally, the group at Los Angeles County retrospectively compared the outcomes of elderly patients (age greater than 65) presenting with acute cholecystitis undergoing early (within 24 h of admission) vs. delayed cholecystectomy (>24 h) [78]. They found no significant differences in postoperative complications, open conversion rates, or in-hospital mortality between the two groups, while anesthesia time and hospital stays were significantly shorter in those patients that had early cholecystectomy. These findings should give surgeons pause to delaying intervention in elderly patients. Furthermore, operative delays also increase the incidence of emergency surgical intervention [74, 75]

with mortality rates as high as 6–15 % [53]. This contrasts with appropriately selected elderly patients that have electively scheduled cholecystectomy and outcomes that are similar to younger patients. Conversely, patients that have a score of more than 3 on the Charlson comorbidity index have been shown to have a 2-year mortality rate of 40.4 % [15], and the PREOP-Gallstone may be helpful in the decision-making process in this patient cohort. Thus, the take-home message should be that age alone should not exclude early operative management in elderly patients presenting with acute cholecystitis.

Some elderly patients with acute cholecystitis will present with severe sepsis and septic shock or have comorbidities that are not optimized which would preclude from undergoing surgical cholecystectomy safely. These patients need to be aggressively treated with admission to the intensive care unit (ICU) and early broad-spectrum antibiotics. Obtaining source control in these patients obviously presents a clinical challenge. Two less invasive procedures, PCT and ERCP, should be considered in these patients once underlying physiologic derangements have been corrected by resuscitation.

PCT can either be done at the patient's bedside under ultrasound guidance or in the fluoroscopy suite. After initial aspiration, a pigtail drainage catheter can be left in place for removal of further infected bile. Cultures of the bile should be sent to tailor empiric antibiotic therapy, particularly if the elderly patient has come from a nursing facility or has received recent antibiotic exposure as this is associated with a higher incidence of resistant organisms that traditional antibiotics may not cover adequately. PTC has excellent efficacy and results in the resolution of sepsis in up to 87 % of critically ill patients, with acceptable 30-day mortality rates [79]. This temporizing measure can allow optimization of the patient's critical illness as well as any other underlying comorbidities. The drainage catheter should be left in place for 6 weeks to allow for establishment of a fibrous fistula tract prior to removal. In certain patients that are a prohibitive surgical risk due to their underlying medical problems, conservative management with PTC cholangiography with stone extraction and catheter removal can be accomplished successfully often without recurrence [61, 80]. In a long-term follow-up study with a mean duration of 3 years, 183 critically ill patients undergoing only PTC for acute cholecystitis had a recurrence rate of only 12 % [57].

ERCP with selective cannulation of the cystic duct and stent placement is another treatment modality that may be particularly useful in critically ill patients that are unable to undergo PCT particularly in the setting of coagulopathy or uncontrolled ascites [81].This procedure is more technically challenging than ERCP and requires advanced endoscopy skills. In experienced hands, this procedure is successful in over 90 % of cases with a reported clinical efficacy of 80–90 % [81].

It should be stressed to the reader that PCT should only be used as a treatment modality in those patients that are too critically ill or medically unfit to undergo a surgical operation as this procedure is associated with increased hospital lengths of stay and up to a 25 % rate of readmission for biliary-related complications. A detailed Cochrane review comparing PCT versus cholecystectomy as initial treatment for severe acute cholecystitis found no evidence to support the use of PCT over surgical intervention [82]. A recent large retrospective single-institution review reached similar conclusions even when accounting for patients that underwent conversion to open cholecystectomy [55]. Those patients that were treated surgically had shorter lengths of stay, as well as a lower number of complications and readmissions compared with those that underwent PCT as treatment for acute cholecystitis. Only those patients that presented with increased comorbidities and medical risk for surgery as defined by the Charlson comorbidity index appeared to benefit from PCT over surgical intervention for acute cholecystitis [55]. Despite this preponderance of evidence, a recent national review by Duszak and Behrman documents a 67 % increase in the use of PCT over the last two decades [83].

Chronic Calculous Cholecystitis

Clinical Presentation and Diagnosis

Chronic cholecystitis is typically the most common manifestation of symptomatic calculous disease and occurs in the setting of multiple (and often insidious) episodes of biliary colic. This scenario is typical in the elderly due to the alterations in pain perception and immune response to inflammation that have been described (see section "Diagnostic Investigation"). The patient often presents with symptoms similar to those of acute cholecystitis without systemic signs of inflammation. Typically the pain is located in the epigastrium/right upper quadrant and is dull or of less intensity due to the absence of acute peritoneal irritation. The patient's temperature, white blood cell count, and liver function tests are most commonly within normal limits. The metabolic panel should also be checked, particularly in the elderly patient, as they often are on medications that can cause fluid and electrolyte derangement. Ultrasonography again should be the initial imaging test of choice that often demonstrates stones within a thickened contracted gallbladder wall. The "double arc" sign is pathognomonic for this condition when seen on ultrasonography [32]. Occasionally chronic cholecystitis will be associated with mural calcification of the gallbladder wall. This may involve a portion of the wall or the entire gallbladder otherwise known as a "porcelain" gallbladder (Fig. 14.10). The significance of this finding has been controversial due to the potential association with

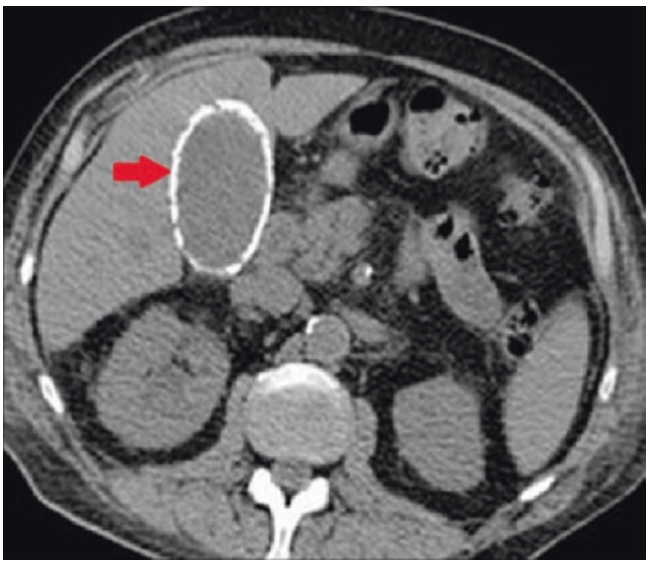

Fig. 14.10 CAT scan of the abdomen showing complete calcification of the gallbladder wall (*arrow*) consistent with a "porcelain" gallbladder

gallbladder carcinoma particularly in the elderly patient [84–86]. Ultrasound findings that are suggestive of this pattern and that show loss of delineation between the gallbladder wall and liver parenchyma where there is no serosal layer should lead one to consider additional diagnostic imaging such as CT or MRI [87].

Treatment of Chronic Calculous Cholecystitis

Once chronic cholecystitis has been diagnosed, initial treatment should be directed at relieving pain symptoms with the judicious use of narcotics. Intravenous fluids should be given as the patient often will be dehydrated from diminished oral intake and may need electrolyte correction. After acute symptoms have resolved, the patient should be risk stratified for surgery. If patients are acceptable candidates, elective laparoscopic cholecystectomy should be undertaken as the natural history of chronic cholecystitis is to recur (40 % chance over 2 years) [88]. Delaying operation because of age and waiting for an episode of recurrence of disease in the elderly are hazardous as they often present in a delayed fashion and with a higher incidence of complicated calculous disease that may require urgent as opposed to elective surgical intervention that is associated with higher morbidity and mortality [26, 53, 70, 88]. Elderly patients may also be considered candidates for same-day discharge or ambulatory cholecystectomy in certain instances, with success rates of 70 %, or more documented in the literature [89].

A special form of chronic cholecystitis that deserves mention is the "porcelain gallbladder." Though the incidence of porcelain gallbladder remains low (0.2 % in a recent large series) [61], there is concern of the potential for malignancy, particularly in those over 50 years of age (incidence of 0.08 %/year of symptoms) [88]. The management of the porcelain gallbladder has undergone considerable change over the past several decades. Early reports suggested a high association between porcelain gallbladder and gallbladder carcinoma (up to 60 %) [90] which led to recommendation of open cholecystectomy once the diagnosis was made. Recently, several large clinical series have questioned the significance of the porcelain gallbladder after finding a much lower incidence of malignancy (0–5 %) [85, 86, 90]. The reasons for this dramatic shift are felt to be due to advances and increased usage of abdominal imaging as most cases of porcelain gallbladder were only diagnosed on plain films of the abdomen, geographic variation of study, and wider usage of laparoscopic cholecystectomy [90].

The overwhelming majority of elderly patients that have a porcelain gallbladder identified on imaging have symptomatic disease which would make them surgical candidates unless their preoperative estimated risk was found to be prohibitive [85, 86, 90]. The asymptomatic patient with incidental findings of a porcelain gallbladder represents a clinical impasse on whether to proceed with operative intervention or observe the patient. The risk of surgical intervention, particularly in the patient with comorbidities, should be balanced against the low potential risk of gallbladder carcinoma and discussed with the patient in order to establish a course of action. Laparoscopic cholecystectomy has been found to be technically feasible in patients with a porcelain gallbladder and should be the initial procedure of choice with more aggressive intervention being reserved for those patients that are found to have cancer on their final pathology or intraoperative findings that are suggestive of carcinoma [90, 91].

Choledocholithiasis

Clinical Presentation and Diagnosis

The majority of common bile duct stones that lead to symptoms originate from the gallbladder itself and can lead to a wide array of clinical symptoms. The elderly population also has a higher incidence of common bile duct stones (range 15–20 %) that present with symptomatic calculous disease compared to younger patients [53]. Up to a third of common duct stones will spontaneously pass into the duodenum [92], while others may lead to common duct obstruction resulting in biliary pancreatitis or cholangitis.

Right upper quadrant pain with abnormal liver function tests is present in over 75 % of patients [93]. The liver panel usually shows a cholestatic (elevated serum bilirubin) pattern, and transaminases may be >500 IU/L along with elevation of alkaline phosphatase or serum gamma-glutamyl transferase (90 % of cases) [94]. Leukocytosis may also be present in the acute phase, and coagulation parameters should be routinely checked as biliary obstruction can lead to transient vitamin K

deficiency and subsequent coagulopathy. It should be noted that around 10 % of patients will be asymptomatic with only mildly elevated liver function tests and common duct stones that are found incidentally on imaging for a reason other than biliary symptoms [93, 95]. In the elderly, malaise, altered mental status, or acute deconditioning may be the only presenting symptoms [62].

Abdominal ultrasonography should be the initial imaging test of choice and has excellent sensitivity for detecting biliary ductal dilation (see Imaging section) and may directly visualize common duct stones. If the ultrasound is normal but clinical and laboratory testing is suggestive of choledocholithiasis, then MRCP should be considered as this has higher sensitivity than sonography. ERCP should generally be reserved for therapeutic purposes due to its invasive risks and technical complications.

Treatment of Choledocholithiasis

Once the diagnosis of choledocholithiasis is made, there are a variety of treatment options available, and these should be tailored based upon local expertise and resource availability. Initial treatment should be directed at alleviating pain, fluid resuscitation, and correction of any electrolyte or coagulation disorders that may be present. Complete removal of common duct stones should be the objective regardless of the intervention chosen because up to 50 % of patients will have recurrence of symptoms if left untreated, and 25 % of these recurrent cases will result in potentially serious complications (i.e., biliary pancreatitis or cholangitis) [94].

Endoscopic therapy with ERCP or percutaneous intervention (PTC) are both acceptable methods of ductal clearance according to the Society for Surgery of the Alimentary Tract (SAGES) and British Society of Gastroenterology guidelines [39, 52] and should be chosen based upon local availability and expertise. As elderly patients are often on anticoagulants or antiplatelet medications, these should be withheld in anticipation of therapeutic intervention. Antibiotics are also typically given periprocedurally and should again be directed primarily against the *Enterobacteriaceae* family. ERCP with balloon dilation of the sphincter has an excellent clinical success rate and appears to be safe even in the elderly population with known comorbidities [40, 53].

Once ductal clearance has been achieved, elderly patients should be offered cholecystectomy if they are acceptable surgical candidates because of the potential for recurrent biliary symptoms. In a 2-year prospective investigation, Lee et al. found that the age and the presence of comorbid conditions were risk factors for recurrence of choledocholithiasis [96]. Additionally, these patients were felt to be at higher surgical risk at the time of recurrent presentation than if they had cholecystectomy at the time of initial presentation. Similar findings were seen in a large systematic review done by the Cochrane group which found a decreased recurrence rate and increased survival advantage even in patients deemed "high risk" were managed with early cholecystectomy as opposed to a "wait and see" approach [97].

The timing of cholecystectomy after ERCP and sphincterotomy has also been investigated prospectively. In a randomized trial comparing "early" laparoscopic cholecystectomy (within 72 h) versus delayed cholecystectomy (6–8 weeks after ERCP), there were no differences in operative duration or rate of conversion to open procedures, while 36 % of patients in the delayed group developed recurrent biliary symptoms [98]. The authors concluded that early cholecystectomy prevented future symptoms related to common duct stones without an increase in morbidity in those undergoing early operation. Patients that undergo ERCP with sphincterotomy and ductal clearance are still at risk for residual choledocholithiasis. Clinical studies assessing this risk in prospective series have found it to be as high as 13 % [99, 100]. Therefore, the authors recommend routine intraoperative cholangiography in patients that had a preoperative ERCP with ductal clearance to reduce the chance of having retained common duct stones (Fig. 14.11). For those surgeons with advanced laparoscopic skills and institutions that have the instrumentation and imaging capability, single-stage procedures to treat choledocholithiasis include laparoscopic cholecystectomy with intraoperative cholangiogram followed by common bile duct exploration have gained

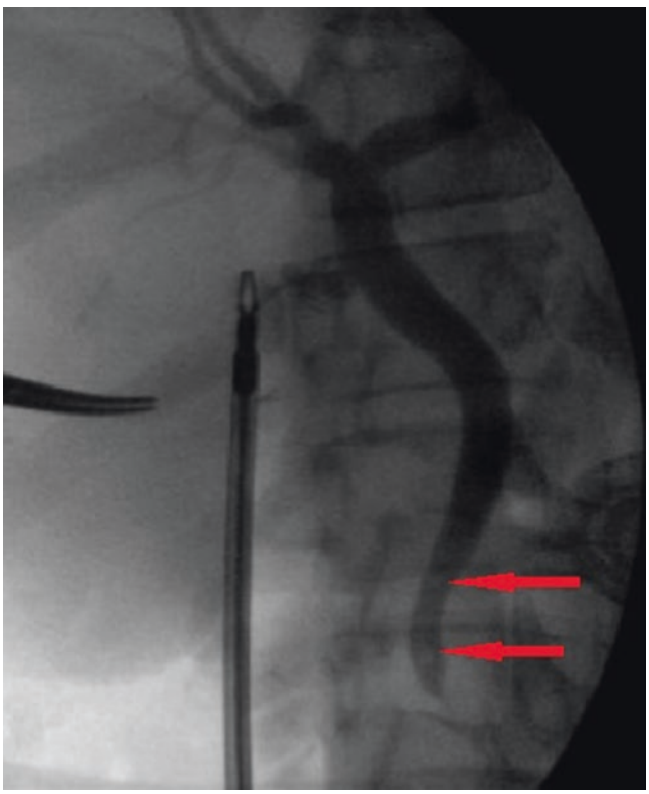

Fig. 14.11 An intraoperative cholangiogram demonstrating two filling defects consistent with common bile duct stones (*arrows*)

popularity. This leads to decreased hospital lengths of stay and total charges without an increase in associated morbidity or mortality [101–103]. This operative approach has also been validated in the elderly and high-risk patients [104]. The benefits of one-stage treatment of choledocholithiasis have only been observed in uncomplicated cases (i.e., no cirrhosis, cholangitis, or biliary sepsis) [101] and with adequate laparoscopic experience [105].

Cholangitis

Clinical Presentation and Diagnosis

Cholangitis can follow a wide spectrum of disease in the elderly patient, from a mild infection to fulminant septic shock with multiple organ dysfunction. Early recognition of which form of disease is present is imperative to achieve good clinical outcomes. An obstructing common duct stone is the most common etiology of cholangitis but may also occur in the presence of benign or malignant biliary strictures. Stasis of bile leads to bacterial overgrowth from the duodenum with *Escherichia coli* being the most common offending organism followed by other members of the family *Enterobacteriaceae*. Increased amounts of pressure in the biliary tree lead to translocation of bacteria into the bloodstream with resultant toxemia [94]. The classic clinical picture of Charcot's triad (fever, right upper quadrant pain, and jaundice) is present in 70 % of patients [94]. The addition of altered mental status changes and hypotension to Charcot's triad form Reynold's pentad and are indicative of suppurative cholangitis, a surgical emergency. In addition to clinical exam findings, laboratory studies often reveal leukocytosis with elevated liver transaminases and cholestasis. Thrombocytopenia, decreased serum bicarbonate (reflective of metabolic acidosis), and elevation of creatinine are diagnostic of more severe cholangitis [106]. Coagulation studies should also be checked in preparation for ductal decompression as biliary obstruction with superimposed sepsis can lead to coagulopathy. Diagnostic imaging is frequently done with ultrasonography that typically reveals dilation of the biliary tree.

Treatment of Cholangitis

Initial therapy should be to establish intravenous access and begin fluid resuscitation followed by early administration of broad-spectrum antibiotics. Appropriate initial antibiotics include third-generation cephalosporins, fluoroquinolones combined with metronidazole, or beta-lactamase inhibitor combinations (i.e., piperacillin/tazobactam) [63]. Blood cultures should be obtained but not delay antibiotic therapy. Since most patients present with mild-moderate cholangitis (nonsuppurative), this will lead to clinical improvement in anticipation of ductal decompression within the next 24 h [52]. Even with initial improvement, elderly patients should be closely monitored for decompensation since age (>50 years) has been shown to be a predictor of poor outcomes [107]. Once sepsis has resolved and the patient is otherwise medically fit, laparoscopic cholecystectomy should be offered to the patient.

For those patients that present with florid sepsis and organ dysfunction, they should be aggressively resuscitated and transferred to the intensive care unit for invasive monitoring. Hemodynamic support with vasopressors may be required in cases of septic shock, and optimization of physiologic parameters should be undertaken to allow for source control through biliary decompression through the least invasive means available. Endoscopic decompression with ERCP has become the initial procedure of choice for most elderly patients [94]. The aim of the procedure is to relieve biliary pressure through minimal manipulation to prevent exacerbation of endotoxemia. Sphincterotomy with biliary stent placement is the most frequently utilized technique. Should ERCP be technically difficult and unsuccessful, external decompression using PTC is a good second-line option. Even with successful decompression, there is still mortality of 5–10 % [108]. In situations where ERCP/PTC is unsuccessful or unavailable, drainage can be accomplished surgically with open common bile duct exploration and T-tube placement. The mortality for this intervention is much higher than the preferred nonsurgical techniques (16–40 %) [93]. After successful biliary decompression and stabilization of the patient, antibiotic therapy should be continued for 14 days and the patient risk stratified for cholecystectomy once optimized from the medical point of view.

Biliary Pancreatitis

Clinical Presentation and Diagnosis

In some cases of choledocholithiasis, the stone transiently lodges at the ampulla and causes an obstruction of the pancreatic duct. This leads to intraductal activation of enzymes and pancreatic glandular damage with a generalized inflammatory response that leads to subsequent symptoms. Risk factors for the development of biliary pancreatitis include advanced age (>60) and female gender [109]. Most cases of biliary pancreatitis are moderate and will resolve with supportive care. However, severe cases of pancreatitis can lead to sepsis and multiple organ dysfunction with mortality rates that exceed 20 % [110] and require a multidisciplinary approach with critical care support.

Clinical symptoms of acute biliary pancreatitis include sharp epigastric pain with radiation to the back that can be confused with aortic dissection or myocardial ischemia in the elderly. Nausea and vomiting are also typically present. Signs of systemic inflammation such as tachycardia and

fever may also be present. In severe cases, the patient can also have hypotension and altered mental status. Helpful laboratory investigations include CBC, serum chemistry with a serum calcium level, liver function tests, and serum amylase and lipase. Leukocytosis is often present secondary to inflammatory response, and the hematocrit is often elevated from hemoconcentration. Serum chemistry can also depict signs of impaired tissue perfusion if the serum bicarbonate is low or renal parameters are indicative of acute renal impairment. Transaminases are often greater than 500 IU/L in the acute phase with a moderate elevation of serum bilirubin. Typically both the serum amylase and lipase will be elevated, but serum amylase declines earlier in the time course of pancreatitis and may be normal in cases of delayed presentation.

Once the diagnosis of biliary pancreatitis is suspected, the initial imaging test should be an abdominal ultrasound. This test can be done even in unstable patients as it can be done at the patient's bedside. Ultrasound is diagnostic of biliary pancreatitis if it reveals calculi or sludge in the gallbladder. Dilation of the biliary tree may also be noted. In patients that are clinically unstable or that do not improve with resuscitation, CT imaging can be helpful in assessing the severity of pancreatitis [111]. The initial study should be non-contrast as it is still clinically useful and avoids exposing a hypovolemic elderly patient to a potentially nephrotoxic contrast load. A CT scan with IV contrast can be obtained at a later time when the patient is clinically stable to delineate areas of potential pancreatic necrosis.

Treatment of Biliary Pancreatitis

Initial therapy is directed at alleviating pain with judicious use of narcotics and nasogastric decompression for those patients presenting with symptoms of ileus. Generous fluid resuscitation should also be undertaken due to the amount of fluid sequestration that can occur in the retroperitoneum. There should be a low threshold to admit elderly patients to the ICU even in moderate cases due to their limited physiologic reserve. Many different scoring systems for determining the severity of pancreatitis have been developed [112–115], but the Ranson score has been shown to have the highest predictive accuracy [113]. A Ranson score of 3 or more is indicative of severe disease. Well-established evidence-based guidelines have been developed for treatment [116, 117].

There are three areas of current debate regarding the optimal therapy of biliary pancreatitis. The first area of controversy in the treatment of severe pancreatitis is the use of prophylactic antibiotics. Several systematic reviews examining the utility of antibiotic prophylaxis in severe acute pancreatitis have been undertaken and have failed to demonstrate any protective benefit on mortality or the risk of developing infected pancreatic necrosis [118–120]. Due to problems with emerging bacterial resistance, the authors recommend against the routine use of antibiotic administration in sterile cases of severe pancreatitis. In instances when superimposed cholangitis is suspected with biliary pancreatitis, appropriate antibiotic therapy is warranted.

Another topic of debate in the management of severe biliary pancreatitis involves the use of early (within 24–48 h) ERCP with sphincterotomy. In the past there has been some literature to support early ERCP in patients with biliary pancreatitis that present with severe disease as or patients with moderate disease that do not exhibit clinical improvement or experience persistent pain [94]. Recently, a meta-analysis reexamined this topic utilizing seven randomized prospective trials (ERCP vs. conservative treatment) in patients that presented with severe biliary pancreatitis without evidence of cholangitis [39]. The authors found that there was no significant benefit or difference in outcome in those patients that underwent early ERCP even when stratifying for disease severity. Therefore, early ductal decompression with ERCP in cases of severe biliary pancreatitis should not be carried out routinely as it provides no significant advantage over general supportive care.

The final area of discussion involves the timing of cholecystectomy after an episode of biliary pancreatitis. As mentioned in the section on choledocholithiasis, the natural history of biliary pancreatitis is recurrence (up to a third of all patients) if the gallbladder is not removed [121]. Each recurrent episode places the patient at risk of life threatening pancreatitis or cholangitis. Recently, the group from Harbor-UCLA investigated the feasibility of early cholecystectomy (within 48 h of admission) in patients presenting with moderate biliary pancreatitis (Ranson <3) and found no apparent increase in perioperative complications and a decreased hospital length of stay compared to those that had an operation after resolution of abdominal pain or improved enzymatic parameters [122]. Other investigations have also found similar findings with the consensus being that laparoscopic cholecystectomy should be performed during the same admission for acute biliary pancreatitis in those patients with acceptable surgical risk [121, 123, 124]. Despite the overwhelming evidence favoring cholecystectomy for biliary pancreatitis, a recent appraisal of this approach in elderly patients showed that over 40 % of patients admitted with a diagnosis of gallstone pancreatitis in a large Medicare sample were not treated surgically with high recurrence rate (33 %) [125]. This clearly leaves room for considerable improvement in caring for elderly patients with symptomatic biliary disease. For patients that are a prohibitive surgical risk due to comorbid illness, ERCP with endoscopic sphincterotomy does provide some protection against recurrence of acute biliary pancreatitis and should be offered to patients that are not surgical candidates [96, 124].

Gallstone Ileus

Clinical Presentation and Diagnosis

Gallstone ileus is classically a disease of the elderly and is an uncommon cause of bowel obstruction (0.1 % in the most recent population-based study [126]) despite its deceptive name. The onset of symptoms is often subtle but may be preceded by symptoms of biliary colic or chronic cholecystitis in approximately 25–75 % of patients [126, 127]. The patient is typically an elderly female (age >70 years) that experiences nausea and vomiting associated with colicky abdominal pain [126]. These symptoms may be fleeting due to transient episodes of obstruction where the stone intermittently lodges and dislodges in narrowed areas of the intestinal tract. This is characteristically known as the "tumbling" phenomenon [128]. The origin of the stones causing the small bowel obstruction is most commonly secondary to the development of a fistula between the gallbladder and duodenum. Other organs involved with development of a fistulous connection are the stomach (cholecystogastric fistula) and transverse colon (cholecystocolonic fistula). Typically the stone causing the obstruction has to be greater than 2.5 cm in size, and the most common site of obstruction is the terminal ileum followed by duodenal-jejunal junction, the duodenal bulb, pyloric region, or sigmoid colon [93]. The classic radiological findings of pneumobilia, ectopic gallstone, and intestinal obstruction observed on plain films of the abdomen (Rigler's triad) are only seen in approximately 50 % of patients (Fig. 14.1) [129]. CT scan is much more sensitive in identifying the diagnosis (93 % sensitivity and 99 % specificity) when obtained [130]. Only 70 % of patients are correctly diagnosed preoperatively with the remainder being diagnosed at the time of operation [127].

Treatment of Gallstone Ileus

As patients that present with this condition are often elderly and debilitated, initial therapy should be directed at fluid resuscitation for dehydration and the correction of any electrolyte abnormalities in preparation for laparotomy. The optimal surgical procedure for this condition continues to be contested. The easiest technical approach involves relief of the obstruction with enterolithotomy, stone removal, examination of the intestine to ensure multiple stones are not present, and closure of the enterotomy. The cholecystoenteric fistula is left in situ to be treated at a later date once the patient is optimized medically or symptoms recur. The second and more aggressive line of treatment involves a one-stage procedure combining enterolithotomy with takedown and closure of the fistula along with cholecystectomy. Lastly, in some cases where there is bowel necrosis, resection is required.

A recent assessment of the operative management of this disease is provided by Halabi, et al. and utilizes the National Inpatient Sample [126]. The authors examined three million cases of bowel obstruction over a four-year period with 0.095 % having gallstone ileus as the source. Three methods of operative therapy were compared: enterolithotomy with stone extraction, enterotomy with stone extraction plus cholecystectomy and fistula closure in one stage, and finally bowel resection alone without fistula closure. Several demographic, hospital, and comorbid factors were taken into consideration when analyzing outcomes, which included hospital lengths of stay, total charges, postoperative morbidities, and in-hospital mortality. Overall mortality was 4.9 % for stone extraction alone compared to 7–13 % for other interventions. Compared to patients undergoing stone extraction alone, more complicated procedures were associated with almost a threefold higher mortality and had twice the risk of complications. Regardless of which surgical approach is considered, it is important to ensure that the entire bowel is checked for multiple stones, which is common in over 25 % of patients [126]. While enterolithotomy is generally associated with less perioperative morbidity and mortality, recurrence of gallstone ileus (5–17 %) and symptomatic biliary disease (5–10 %) [129] remain potential problems. Autopsy findings of patients that have undergone enterolithotomy alone have demonstrated that the fistulous connection between the biliary tree and GI tract can close spontaneously in the absence of cholelithiasis [131]. Additionally, elective resection is associated with a lower incidence of complications and postoperative mortality [126]. While enterolithotomy is the preferred procedure by most experts, this condition is relatively rare, and no large randomized studies are available to compare the superiority of one procedure over another [129]. No Level I data exists regarding the treatment of this condition; thus surgical therapy should be tailored individually based upon the patient's global condition as well as intraoperative findings.

Benign Acalculous Diseases

Acute Acalculous Cholecystitis

Clinical Presentation and Diagnosis

Acalculous cholecystitis represents 5–10 % of acute gallbladder pathology in adults [93]. Predisposing risk factors include advanced age, presence of comorbidities, and critical illness. This illness generally occurs in patients over 60 years of age and within the second to fifth week of critical illness [132]. Common predisposing conditions include postoperative complex cardiac and vascular patients as well as those whom have suffered major burns, trauma, or cardiac arrest [133]. The etiology is multifactorial but thought to be related to biliary stasis [133] and systemic hypoperfusion leading to gallbladder ischemia with bacterial overgrowth. Despite

increased awareness of this disease entity, mortality rates continue to be as high as 30 % [133].

A high index of suspicion is necessary to diagnose acute acalculous cholecystitis; due to the patient's often debilitated state, they are unable to communicate pain, and the presence of sepsis and with leukocytosis and liver function abnormalities is common in many critically ill patients. Abdominal ultrasound is the most useful imaging test with gallbladder wall thickening being the most common diagnostic finding. The sensitivity of ultrasound for diagnosis can vary widely from 29 to 92 % [132] due to false-positive exams that can occur with ascites or other inflammatory conditions. HIDA can also be used for the diagnosis in cases of high suspicion when the ultrasound is equivocal with sensitivity that ranges from 67 to 100 % [132]. The downside of this diagnostic test is that it often requires patients to be transported from the ICU for an extended period of time although some centers have portable units that are capable of performing this test at the patient's bedside.

Treatment of Acalculous Cholecystitis

Once the diagnosis has been made or clinical suspicion is high enough, PCT is the treatment of choice due to the debilitated state of the patient. Typically patients are already on empiric antibiotics for their critical illness, and coverage should include the same organisms that are responsible for acute cholecystitis. Cholecystostomy tube placement can either be performed at the patient's bedside under ultrasonography or under fluoroscopy with either procedure being clinically effective for resolution of sepsis [79]. Surgical intervention is reserved only for those patients that do not respond to percutaneous intervention. In a study comparing outcomes, using bridging cholecystostomy followed by elective cholecystectomy vs. open cholecystectomy showed decreased mortality and shorter recovery times in those patients treated by initial PTC [134]. Once drainage has been accomplished, the cholecystostomy tube can be left in place for 4–6 weeks to allow a tract to establish and patient to convalesce. A repeat cholangiogram can then be performed (Fig. 14.12) to document gallbladder drainage through the cystic duct. If this is the case, the cholecystostomy tube can often be removed without worry of recurrence once the patient recovers from their critical illness and elective cholecystectomy considered.

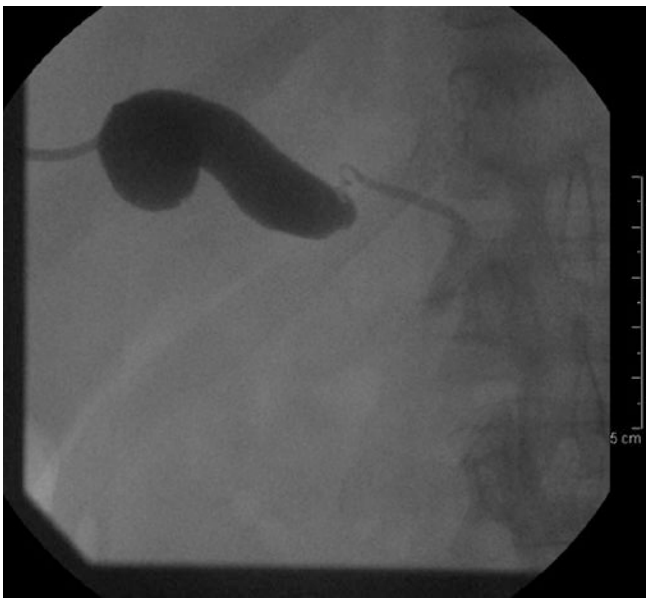

Fig. 14.12 PTC cholangiogram done after convalescence from critical illness secondary to acalculous cholecystitis. Notice the patency of the cystic duct with passage of contrast into the common bile duct

Motility Disorders of the Biliary Tree

Clinical Presentation and Diagnosis

Motility disorders of the biliary tree include biliary dyskinesia as well as sphincter of Oddi dysfunction. The hallmark of both disorders is a constellation of classically biliary type symptoms: epigastric or right upper quadrant pain that is episodic and severe enough to interrupt the patient's daily life as defined by the Rome committee [135].

In biliary dyskinesia laboratory investigations and imaging studies are normal and no other etiology for the patient's pain can be discovered. The diagnosis of biliary dyskinesia is made exclusively with the use of biliary scintigraphy with cholecystokinin infusion in order to determine the patient's gallbladder ejection fraction (EF). Normal gallbladder EF is around 70 %, while studies are considered abnormal when the EF is less than 50 % or the infusion of cholecystokinin reproduces the patient's pain symptoms [136]. It should be noted that certain medications that are common in elderly patients (i.e., calcium channel blockers and opiates) could also cause impaired gallbladder ejection fraction and cause an abnormal scintigraphy scan [136].

Sphincter of Oddi dysfunction can present as either recurrent attacks of abdominal pain that mimic biliary colic, as recurrent idiopathic pancreatitis, or as postcholecystectomy pain. The most classic form of sphincter of Oddi dysfunction is a triad of biliary colic, abnormal liver function tests, and documentation of a dilated common bile duct on imaging without any evidence of gallstones [137]. The diagnostic work-up [138] should consist of endoscopy with ultrasonography as this may document stones that are not seen on traditional ultrasonography or other imaging modalities. If this is negative, then ERCP should be done to rule out microlithiasis and sphincter manometry performed. Elevated basal sphincter pressures or paradoxical spasm noted with cholecystokinin infusion are suggestive of the diagnosis.

Treatment of Biliary Motility Disorders

Biliary dyskinesia is treated by laparoscopic cholecystectomy in acceptable risk patients with some specimens revealing microlithiasis or stones that were missed by sonography. Symptom relief after cholecystectomy ranges from 70 to 90 % of patients [139, 140]. Patients that have typical biliary symptoms, an abnormal gallbladder EF, or occult cholelithiasis have the best postoperative results [136].

Sphincter of Oddi dysfunction is treated by endoscopic sphincterotomy of both the biliary and pancreatic ducts [141] although a trial of medical management may be undertaken first with medications such as calcium channel blockers or anticholinergics [138, 142]. For patients that have an inaccessible papilla or a recurrence of symptoms after sphincterotomy, open transduodenal sphincterotomy is an option [143]. The efficacy of sphincterotomy varies widely from 20 to 91 %, with those patients that have elevated basal pressures on manometry with classic biliary colic pain achieving the best results [137, 138].

Neoplasms of the Gallbladder

Gallbladder Polyps

Clinical Presentation and Diagnosis

Polyps of the gallbladder are observed in about 5 % of patients that undergo abdominal ultrasound [144] with most patients being asymptomatic (77 %) [145] and imaged for another reason. The majority of these documented polyps are pseudopolyps with the majority being cholesterol polyps or adenomyomatosis (85 %) followed by inflammatory polyps (10 %) with the remainder being true polyps that are predominantly either adenomas or adenocarcinomas [146].

True polyps are the only form of polyps with malignant potential. Polyp size, vascularity, rate of growth, Asian descent, and patient age have been linked to malignant potential [146, 147]. Cholelithiasis was originally thought to be associated with polyp development and malignancy; however several authors have documented that this is not the case [145, 148]. The most commonly cited size that is associated with a risk for malignancy is 10 mm. Using this size cutoff, Koga analyzed polyps found in cholecystectomy specimens and observed that 88 % of malignant polyps were greater than 10 mm in size [149]. This size criterion has been challenged due to malignancy being found in polyps of smaller size. A Mayo Clinic study showed that polyps under 10 mm carried a 7.4 % chance of malignancy and that a size greater than 6 mm was a risk factor for malignancy [150]. Using this reduced size cutoff on ultrasound resulted in 100 % negative predictive value. It should be noted that sonography has been shown to overestimate lesion size by 4 cm or more and that may have a false-positive rate as high as 22 % [147]. Also, more recent data examining cholecystectomy specimens have found that no cancers have arisen in polyps that are less than 2 cm in size [151] and that in the US population the progression from adenoma is exceedingly rare and routine imaging is not warranted for polyps less than 10 mm [147].

As previously mentioned, age is also a risk factor for polyp malignancy. Two separate studies have shown that patient age over 50 has a significantly higher chance of being associated with a malignant polyp [152, 153]. Based upon the patient's age and size of polyp, the patient can be risk stratified into low or high risk for neoplasm. Endoscopic ultrasound may provide assistance in intermediate cases based upon clinical scoring features of the polyp due to the superior imaging provided as well as opportunity for biopsy by some endoscopists [43, 154, 155].

Treatment of Gallbladder Polyps

In patients that are symptomatic (i.e., biliary colic) without another identifiable etiology for the pain, laparoscopic cholecystectomy should be offered [146]. Polyps that are greater than 10 mm in size without symptoms should also be treated with laparoscopic cholecystectomy unless the polyp is greater than 1.8 cm in size [146]. Two different series have shown that polyps above this size are often associated with an invasive cancer, and an open cholecystectomy should be considered with partial liver resection and lymphadenectomy if necessary based upon the depth of invasion (see section "Gallbladder Carcinoma") [96, 156, 157]. For asymptomatic lesions that are 6–10 mm, watchful waiting along with serial abdominal ultrasound examinations has been proven to be a safe treatment strategy keeping in mind that there may be a high false-positive rate [145, 148]. Polyp growth has been observed in 6 % of patients according to one 11-year retrospective study (*Ito*). Though there are not any well-established guidelines regarding the interval of screening, most experts favor imaging every 6–12 months [148, 158]. Lesions that are of intermediate size (6–10 mm) represent a treatment challenge given evidence that neoplastic growth may occur at polyp sizes in this range and conflicting data regarding the malignant potential of gallbladder polyps. In these cases endoscopic ultrasonography may be helpful to determine which lesions are suspicious enough to warrant cholecystectomy [146].

Gallbladder Carcinoma

Clinical Presentation and Diagnosis

Although uncommon, gallbladder carcinoma is the most common cancer of the biliary tree with the overwhelming majority of cases being adenocarcinoma (80 %) [159]. Approximately 10 % of these malignancies are diagnosed in cholecystectomy specimens [159]. The incidence in the

United States is 1.2/100,000 with the malignancy occurring more frequently in other countries. Risk factors include advanced age (>65), female gender, obesity, and those of Asian descent [160]. As previously mentioned, cholelithiasis was previously thought to be a causal factor in the development of gallbladder carcinoma, but recent data suggests otherwise.

Unfortunately most cases are asymptomatic or have nonspecific complaints leading to delayed presentation at an inoperable stage (50 %) [161]. Other patients may present with typical biliary symptoms and have undergone cholecystectomy with incidentally discovered cancer in the removed specimen (10 %) or have undergone abdominal imaging for another indication revealing gallbladder findings that are concerning for malignancy (i.e., large polyps or mass with liver involvement) [159].

In the patients where gallbladder cancer is suspected preoperatively, a CT of the abdomen should be obtained to assess for tumor invasion into the liver or other organs as well as lymph node involvement [161]. Findings on CT that preclude curative resection include: invasion of the common hepatic artery or main portal vein, lymph node involvement outside the hepatic hilum, or obvious evidence of metastasis [159]. Assessing the thickness of the gallbladder wall is also important, as this is the most common imaging finding in gallbladder carcinoma. A wall thickness of greater than 10 mm with strong mucosal enhancement strongly suggests the presence of cancer [147]. A recent report assessing the diagnostic ability of PET imaging in patients with suspected gallbladder carcinoma showed an accuracy of 96 % for identifying the primary lesion and 86 % percent for identifying nodal involvement [162]. This can allow for accurate preoperative staging, as lesions that have portal vascular involvement or nodal metastasis away from the hepatic hilum are considered non-resectable. Most patients with the diagnosis are often elderly with comorbidities, and a reasonable assessment of functional liver reserve should be done to ensure that a large liver resection would not lead to acute fulminant hepatic failure.

Treatment of Gallbladder Carcinoma

In cases where the diagnosis of gallbladder cancer is known or suspected preoperatively, an open cholecystectomy with wedge resection of the liver as well as portal lymphadenectomy should be the planned procedure [163]. Diagnostic laparoscopy may be considered prior to laparotomy as this can identify peritoneal disease or noncontiguous hepatic involvement not seen on preoperative imaging that would preclude curative resection in almost 50 % of patients [164]. Once the specimen is excised, the cystic duct margin should also be sent and if positive be followed by an excision of the common bile duct with hepatico-jejunostomy reconstruction [161]. Margins of the liver wedge resection should also be checked and if positive be extended surgically until negative margins are obtained [163]. Some tumors require formal anatomic liver resection (Couinaud segments IV and V), but this is usually known preoperatively.

Commonly patients that have undergone cholecystectomy for presumed benign disease will have the tumor identified on final pathology. Tumors that are found to be in situ or only invade the lamina propria (T1a) are considered cured with 5-year survival rates of greater than 90 % [159]. All other tumors with more extensive invasion should undergo reoperation with wedge resection of the liver, lymphadenectomy, and possible common bile duct excision [163]. Laparoscopic port site excision was once considered mandatory; however, while port site metastasis is common (19 %), routine excision does not increase the 5-year survival [165]. Once the tumor extends into the peri-muscular connective tissue of the gallbladder or there is lymph node involvement, the 5-year survival decreases dramatically even with attempts at curative resection as adjuvant chemotherapy and radiation remain ineffective [163, 166]. This should be kept in mind when considering extensive resections in the elderly patient. In patients that present with unresectable disease and biliary obstruction, endoscopic or percutaneous interventions with biliary stenting are often successful at providing palliation [53, 163].

References

1. Sanson TG, O'Keefe KP. Evaluation of abdominal pain in the elderly. Emerg Med Clin North Am. 1996;14(3):615–27.
2. Friedman GD, Kannel WB, Dawber TR. The epidemiology of gallbladder disease: observations in the Framingham Study. J Chronic Dis. 1966;19(3):273–92.
3. Lirussi F, Nassuato G, Passera D, Toso S, Zalunardo B, Monica F, et al. Gallstone disease in an elderly population: the Silea study. Eur J Gastroenterol Hepatol. 1999;11(5):485–91.
4. Ratner J, Lisbona A, Rosenbloom M, Palayew M, Szabolcsi S, Tupaz T. The prevalence of gallstone disease in very old institutionalized persons. JAMA. 1991;265(7):902–3.
5. Brewer BJ, Golden GT, Hitch DC, Rudolf LE, Wangensteen SL. Abdominal pain. An analysis of 1,000 consecutive cases in a University Hospital emergency room. Am J Surg. 1976;131(2):219–23.
6. Urbach DR, Stukel TA. Rate of elective cholecystectomy and the incidence of severe gallstone disease. CMAJ. 2005;172(8):1015–9.
7. Estellar A. Physiology of bile secretion. World J Gastroenterol. 2008;14(37):8.
8. Shaffer EA. The effect of vagotomy on gallbladder function and bile composition in man. Ann Surg. 1982;195(4):413–8.
9. Banfield WJ. Physiology of the gallbladder. Gastroenterology. 1975;69(3):770–7.
10. Attili AF, Carulli N, Roda E, Barbara B, Capocaccia L, Menotti A, et al. Epidemiology of gallstone disease in Italy: prevalence data of the Multicenter Italian Study on Cholelithiasis (M.I.COL.). Am J Epidemiol. 1995;141(2):158–65.
11. Shah BB, Agrawal RM, Goldwasser B, Farah KF. Biliary diseases in the elderly. Pract Gastroenterol. 2008;32(9):9.
12. Walsh RM. Innovations in treating the elderly who have biliary and pancreatic disease. Clin Geriatr Med. 2006;22(3):545–58.

13. Kahng KU, Roslyn JJ. Surgical issues for the elderly patient with hepatobiliary disease. Surg Clin North Am. 1994;74(2):345–73.
14. Fry DE, Pine M, Pine G. Ninety-day postdischarge outcomes of inpatient elective laparoscopic cholecystectomy. Surgery. 2014;156(4):931–6.
15. Parmar AD, Sheffield KM, Adhikari D, Davee RA, Vargas GM, Tamirisa NP, et al. PREOP-gallstones: a prognostic nomogram for the management of symptomatic cholelithiasis in older patients. Ann Surg. 2015;261(6):1184–90.
16. Eagle KA, Brundage BH, Chaitman BR, Ewy GA, Fleisher LA, Hertzer NR, et al. Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery. Circulation. 1996;93(6):1278–317.
17. Jin F, Chung F. Minimizing perioperative adverse events in the elderly. Br J Anaesth. 2001;87(4):608–24.
18. Goldman L, Caldera DL, Nussbaum SR, Southwick FS, Krogstad D, Murray B, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med. 1977;297(16):845–50.
19. Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ. 2005;173(6):627–34.
20. Wijeysundera DN, Duncan D, Nkonde-Price C, Virani SS, Washam JB, Fleischmann KE, et al. Perioperative beta blockade in noncardiac surgery: a systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014;64(22):2406–25.
21. Vaughan MS, Vaughan RW, Cork RC. Postoperative hypothermia in adults: relationship of age, anesthesia, and shivering to rewarming. Anesth Analg. 1981;60(10):746–51.
22. Frank SM, Higgins MS, Breslow MJ, Fleisher LA, Gorman RB, Sitzmann JV, et al. The catecholamine, cortisol, and hemodynamic responses to mild perioperative hypothermia. A randomized clinical trial. Anesthesiology. 1995;82(1):83–93.
23. Haley RW, Culver DH, Morgan WM, White JW, Emori TG, Hooton TM. Identifying patients at high risk of surgical wound infection. A simple multivariate index of patient susceptibility and wound contamination. Am J Epidemiol. 1985;121(2):206–15.
24. Ballantyne JC, Carr DB, deFerranti S, Suarez T, Lau J, Chalmers TC, et al. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. Anesth Analg. 1998;86(3):598–612.
25. Rosenthal RA, Andersen DK. Surgery in the elderly: observations on the pathophysiology and treatment of cholelithiasis. Exp Gerontol. 1993;28(4-5):459–72.
26. Martinez JP, Mattu A. Abdominal pain in the elderly. Emerg Med Clin North Am 2006;24(2):371–88, vii.
27. Cooper GS, Shlaes DM, Salata RA. Intraabdominal infection: differences in presentation and outcome between younger patients and the elderly. Clin Infect Dis. 1994;19(1):146–8.
28. Bedirli A, Sakrak O, Sozuer EM, Kerek M, Guler I. Factors effecting the complications in the natural history of acute cholecystitis. Hepato-Gastroenterology. 2001;48(41):1275–8.
29. Garcea G, Ngu W, Neal CP, Dennison AR, Berry DP. Bilirubin levels predict malignancy in patients with obstructive jaundice. HPB (Oxford). 2011;13(6):426–30.
30. Potter J, Klipstein K, Reilly JJ, Roberts M. The nutritional status and clinical course of acute admissions to a geriatric unit. Age Ageing. 1995;24(2):131–6.
31. Stewart L, Griffiss JM, Way LW. Spectrum of gallstone disease in the veterans population. Am J Surg. 2005;190(5):746–51.
32. Gore RM, Thakrar KH, Newmark GM, Mehta UK, Berlin JW. Gallbladder imaging. Gastroenterol Clin N Am 2010;39(2):265–87, ix.
33. Laing FC. Diagnostic evaluation of patients with suspected acute cholecystitis. Radiol Clin N Am. 1983;21(3):477–93.
34. Laing F. The gallbladder and bile ducts. Rumack CW, Wilson S, Charboneau J, editor. St. Louis: Mosby Yearbook; 1998. 48 p.
35. Spence SC, Teichgraeber D, Chandrasekhar C. Emergent right upper quadrant sonography. J Ultrasound Med. 2009;28(4):479–96.
36. Rybicki FJ. The WES sign. Radiology. 2000;214(3):881–2.
37. Millat B, Decker G, Fingerhut A. Imaging of cholelithiasis: what does the surgeon need? Abdom Imaging. 2001;26(1):3–6.
38. O'Neill DE, Saunders MD. Endoscopic ultrasonography in diseases of the gallbladder. Gastroenterol Clin N Am 2010;39(2):289–305, ix.
39. Petrov MS, Savides TJ. Systematic review of endoscopic ultrasonography versus endoscopic retrograde cholangiopancreatography for suspected choledocholithiasis. Br J Surg. 2009;96(9):967–74.
40. Benson ME, Byrne S, Brust DJ, Manning 3rd B, Pfau PR, Frick TJ, et al. EUS and ERCP complication rates are not increased in elderly patients. Dig Dis Sci. 2010;55(11):3278–83.
41. Lin EC, Kuni CC. Radionuclide imaging of hepatic and biliary disease. Semin Liver Dis. 2001;21(2):179–94.
42. Carroll BA. Preferred imaging techniques for the diagnosis of cholecystitis and cholelithiasis. Ann Surg. 1989;210(1):1–12.
43. Sugiyama M, Atomi Y, Yamato T. Endoscopic ultrasonography for differential diagnosis of polypoid gall bladder lesions: analysis in surgical and follow up series. Gut. 2000;46(2):250–4.
44. Stoker J, van Randen A, Lameris W, Boermeester MA. Imaging patients with acute abdominal pain. Radiology. 2009;253(1):31–46.
45. Furlan A, Ferris JV, Hosseinzadeh K, Borhani AA. Gallbladder carcinoma update: multimodality imaging evaluation, staging, and treatment options. AJR Am J Roentgenol. 2008;191(5):1440–7.
46. Schweiger MJ, Chambers CE, Davidson CJ, Blankenship J, Bhalla NP, Block PC, et al. Prevention of contrast induced nephropathy: recommendations for the high risk patient undergoing cardiovascular procedures. Catheter Cardiovasc Interv. 2007;69(1):135–40.
47. Shakespear JS, Shaaban AM, Rezvani M. CT findings of acute cholecystitis and its complications. AJR Am J Roentgenol. 2010;194(6):1523–9.
48. Tsai HM, Lin XZ, Chen CY, Lin PW, Lin JC. MRI of gallstones with different compositions. AJR Am J Roentgenol. 2004;182(6):1513–9.
49. Hekimoglu K, Ustundag Y, Dusak A, Erdem Z, Karademir B, Aydemir S, et al. MRCP vs. ERCP in the evaluation of biliary pathologies: review of current literature. J Dig Dis. 2008;9(3):162–9.
50. Irie H, Honda H, Kuroiwa T, Yoshimitsu K, Aibe H, Shinozaki K, et al. Pitfalls in MR cholangiopancreatographic interpretation. Radiographics. 2001;21(1):23–37.
51. Nazarian S, Hansford R, Roguin A, Goldsher D, Zviman MM, Lardo AC, et al. A prospective evaluation of a protocol for magnetic resonance imaging of patients with implanted cardiac devices. Ann Intern Med. 2011;155(7):415–24.
52. Williams EJ, Green J, Beckingham I, Parks R, Martin D, Lombard M, et al. Guidelines on the management of common bile duct stones (CBDS). Gut. 2008;57(7):1004–21.
53. Siegel JH, Kasmin FE. Biliary tract diseases in the elderly: management and outcomes. Gut. 1997;41(4):433–5.
54. Sugiyama M, Atomi Y. Endoscopic sphincterotomy for bile duct stones in patients 90 years of age and older. Gastrointest Endosc. 2000;52(2):187–91.
55. Abi-Haidar Y, Sanchez V, Williams SA, Itani KM. Revisiting percutaneous cholecystostomy for acute cholecystitis based on a 10-year experience. Arch Surg. 2012;147(5):416–22.
56. Elyaderani MK, McDowell DE, Gabriele OF. A preliminary report of percutaneous cholecystostomy under ultrasonography and fluoroscopy guidance. J Clin Gastroenterol. 1983;5(3):277–81.

57. Chang YR, Ahn YJ, Jang JY, Kang MJ, Kwon W, Jung WH, et al. Percutaneous cholecystostomy for acute cholecystitis in patients with high comorbidity and re-evaluation of treatment efficacy. Surgery. 2014;155(4):615–22.
58. Vogt DP. Gallbladder disease: an update on diagnosis and treatment. Cleve Clin J Med. 2002;69(12):977–84.
59. Joseph T, Unver K, Hwang GL, Rosenberg J, Sze DY, Hashimi S, et al. Percutaneous cholecystostomy for acute cholecystitis: ten-year experience. J Vasc Interv Radiol 2012;23(1):83–8 e1.
60. Morrow DJ, Thompson J, Wilson SE. Acute cholecystitis in the elderly: a surgical emergency. Arch Surg. 1978;113(10):1149–52.
61. Strasberg SM. Clinical practice. Acute calculous cholecystitis. N Engl J Med. 2008;358(26):2804–11.
62. Cobden I, Lendrum R, Venables CW, James OF. Gallstones presenting as mental and physical debility in the elderly. Lancet. 1984;1(8385):1062–4.
63. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect. 2010;11(1):79–109.
64. Keus F, de Jong JA, Gooszen HG, van Laarhoven CJ. Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis. Cochrane Database Syst Rev. 2006;(4):CD006231.
65. Yamashita Y, Takada T, Kawarada Y, Nimura Y, Hirota M, Miura F, et al. Surgical treatment of patients with acute cholecystitis: Tokyo Guidelines. J Hepato-Biliary-Pancreat Surg. 2007;14(1):91–7.
66. Overby DW, Apelgren KN, Richardson W, Fanelli R, Society of American G, Endoscopic S. SAGES guidelines for the clinical application of laparoscopic biliary tract surgery. Surg Endosc. 2010;24(10):2368–86.
67. de Mestral C, Rotstein OD, Laupacis A, Hoch JS, Zagorski B, Nathens AB. A population-based analysis of the clinical course of 10,304 patients with acute cholecystitis, discharged without cholecystectomy. J Trauma Acute Care Surg. 2013;74(1):26–30; discussion 1.
68. Gurusamy KS, Samraj K. Early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Cochrane Database Syst Rev. 2006;(4):CD005440.
69. Ransohoff DF, Gracie WA. Treatment of gallstones. Ann Intern Med. 1993;119(7 Pt 1):606–19.
70. Bergman S, Sourial N, Vedel I, Hanna WC, Fraser SA, Newman D, et al. Gallstone disease in the elderly: are older patients managed differently? Surg Endosc. 2011;25(1):55–61.
71. Gurusamy K, Samraj K, Gluud C, Wilson E, Davidson BR. Meta-analysis of randomized controlled trials on the safety and effectiveness of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Br J Surg. 2010;97(2):141–50.
72. Siddiqui T, MacDonald A, Chong PS, Jenkins JT. Early versus delayed laparoscopic cholecystectomy for acute cholecystitis: a meta-analysis of randomized clinical trials. Am J Surg. 2008;195(1):40–7.
73. Flum DR, Cheadle A, Prela C, Dellinger EP, Chan L. Bile duct injury during cholecystectomy and survival in medicare beneficiaries. JAMA. 2003;290(16):2168–73.
74. Arthur JD, Edwards PR, Chagla LS. Management of gallstone disease in the elderly. Ann R Coll Surg Engl. 2003;85(2):91–6.
75. Chareton B, Letoquart JP, Lucas A, La Gamma A, Kunin N, Chaillou M, et al. Cholelithiasis in patients over 75 years of age. Apropos of 147 cases. J Chir (Paris). 1991;128(10):399–402.
76. Cull JD, Velasco JM, Czubak A, Rice D, Brown EC. Management of acute cholecystitis: prevalence of percutaneous cholecystostomy and delayed cholecystectomy in the elderly. J Gastrointest Surg. 2014;18(2):328–33.
77. Riall TS, Zhang D, Townsend Jr CM, Kuo YF, Goodwin JS. Failure to perform cholecystectomy for acute cholecystitis in elderly patients is associated with increased morbidity, mortality, and cost. J Am Coll Surg. 2010;210(5):668–77.
78. Haltmeier T, Benjamin E, Inaba K, Lam L, Demetriades D. Early versus delayed same-admission laparoscopic cholecystectomy for acute cholecystitis in elderly patients with comorbidities. J Trauma Acute Care Surg. 2015;78(4):801–7.
79. Chok KS, Chu FS, Cheung TT, Lam VW, Yuen WK, Ng KK, et al. Results of percutaneous transhepatic cholecystostomy for high surgical risk patients with acute cholecystitis. ANZ J Surg. 2010;80(4):280–3.
80. Van Steenbergen W, Ponette E, Marchal G, Pelemans W, Aerts R, Fevery J, et al. Percutaneous transhepatic cholecystostomy for acute complicated cholecystitis in elderly patients. Am J Gastroenterol. 1990;85(10):1363–9.
81. Itoi T, Sofuni A, Itokawa F, Tsuchiya T, Kurihara T, Ishii K, et al. Endoscopic transpapillary gallbladder drainage in patients with acute cholecystitis in whom percutaneous transhepatic approach is contraindicated or anatomically impossible (with video). Gastrointest Endosc. 2008;68(3):455–60.
82. Winbladh A, Gullstrand P, Svanvik J, Sandstrom P. Systematic review of cholecystostomy as a treatment option in acute cholecystitis. HPB (Oxford). 2009;11(3):183–93.
83. Duszak Jr R, Behrman SW. National trends in percutaneous cholecystostomy between 1994 and 2009: perspectives from Medicare provider claims. J Am Coll Radiol. 2012;9(7):474–9.
84. Polk Jr HC. Carcinoma and the calcified gall bladder. Gastroenterology. 1966;50(4):582–5.
85. Stephen AE, Berger DL. Carcinoma in the porcelain gallbladder: a relationship revisited. Surgery. 2001;129(6):699–703.
86. Towfigh S, McFadden DW, Cortina GR, Thompson Jr JE, Tompkins RK, Chandler C, et al. Porcelain gallbladder is not associated with gallbladder carcinoma. Am Surg. 2001;67(1):7–10.
87. Levy AD, Murakata LA, Rohrmann CA, Jr. Gallbladder carcinoma: radiologic-pathologic correlation. Radiographics. 2001;21(2):295–314; questionnaire, 549–55.
88. Thistle JL, Cleary PA, Lachin JM, Tyor MP, Hersh T. The natural history of cholelithiasis: the National Cooperative Gallstone Study. Ann Intern Med. 1984;101(2):171–5.
89. Ahmad NZ, Byrnes G, Naqvi SA. A meta-analysis of ambulatory versus inpatient laparoscopic cholecystectomy. Surg Endosc. 2008;22(9):1928–34.
90. Khan ZS, Livingston EH, Huerta S. Reassessing the need for prophylactic surgery in patients with porcelain gallbladder: case series and systematic review of the literature. Arch Surg. 2011;146(10):1143–7.
91. Kim JH, Kim WH, Yoo BM, Kim JH, Kim MW. Should we perform surgical management in all patients with suspected porcelain gallbladder? Hepato-Gastroenterology. 2009;56(93):943–5.
92. Elmi F, Silverman WB. Long-term biliary endoscopic sphincterotomy restenosis: incidence, endoscopic management, and complications of retreatment. Dig Dis Sci. 2010;55(7):2102–7.
93. Dooley J. Gallstones and benign biliary diseases. 12th ed. Dooley JL, Burrough A, Heathcote E, editor. Blackwell Publishing; 2011.
94. Attasaranya S, Fogel EL, Lehman GA. Choledocholithiasis, ascending cholangitis, and gallstone pancreatitis. Med Clin North Am 2008;92(4):925–60, x.
95. Tazuma S. Gallstone disease: epidemiology, pathogenesis, and classification of biliary stones (common bile duct and intrahepatic). Best Pract Res Clin Gastroenterol. 2006;20(6):1075–83.
96. Lee JK, Ryu JK, Park JK, Yoon WJ, Lee SH, Hwang JH, et al. Roles of endoscopic sphincterotomy and cholecystectomy in acute biliary pancreatitis. Hepato-Gastroenterology. 2008;55(88):1981–5.
97. McAlister VC, Davenport E, Renouf E. Cholecystectomy deferral in patients with endoscopic sphincterotomy. Cochrane Database Syst Rev. 2007;(4):CD006233.

98. Reinders JS, Goud A, Timmer R, Kruyt PM, Witteman BJ, Smakman N, et al. Early laparoscopic cholecystectomy improves outcomes after endoscopic sphincterotomy for choledochocystolithiasis. Gastroenterology. 2010;138(7):2315–20.
99. Edye M, Dalvi A, Canin-Endres J, Baskin-Bey E, Salky B. Intraoperative cholangiography is still indicated after preoperative endoscopic cholangiography for gallstone disease. Surg Endosc. 2002;16(5):799–802.
100. Pierce RA, Jonnalagadda S, Spitler JA, Tessier DJ, Liaw JM, Lall SC, et al. Incidence of residual choledocholithiasis detected by intraoperative cholangiography at the time of laparoscopic cholecystectomy in patients having undergone preoperative ERCP. Surg Endosc. 2008;22(11):2365–72.
101. Kharbutli B, Velanovich V. Management of preoperatively suspected choledocholithiasis: a decision analysis. J Gastrointest Surg. 2008;12(11):1973–80.
102. Rogers SJ, Cello JP, Horn JK, Siperstein AE, Schecter WP, Campbell AR, et al. Prospective randomized trial of LC+LCBDE vs ERCP/S+LC for common bile duct stone disease. Arch Surg. 2010;145(1):28–33.
103. Schroeppel TJ, Lambert PJ, Mathiason MA, Kothari SN. An economic analysis of hospital charges for choledocholithiasis by different treatment strategies. Am Surg. 2007;73(5):472–7.
104. Noble H, Tranter S, Chesworth T, Norton S, Thompson M. A randomized, clinical trial to compare endoscopic sphincterotomy and subsequent laparoscopic cholecystectomy with primary laparoscopic bile duct exploration during cholecystectomy in higher risk patients with choledocholithiasis. J Laparoendosc Adv Surg Tech A. 2009;19(6):713–20.
105. O'Neill CJ, Gillies DM, Gani JS. Choledocholithiasis: overdiagnosed endoscopically and undertreated laparoscopically. ANZ J Surg. 2008;78(6):487–91.
106. Kiriyama S, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Pitt HA, et al. New diagnostic criteria and severity assessment of acute cholangitis in revised Tokyo Guidelines. J Hepatobiliary Pancreat Sci. 2012;19(5):548–56.
107. Gigot JF, Leese T, Dereme T, Coutinho J, Castaing D, Bismuth H. Acute cholangitis. Multivariate analysis of risk factors. Ann Surg. 1989;209(4):435–8.
108. Leung JW, Chung SC, Sung JJ, Banez VP, Li AK. Urgent endoscopic drainage for acute suppurative cholangitis. Lancet. 1989;1(8650):1307–9.
109. Whitcomb DC. Clinical practice. Acute pancreatitis. N Engl J Med. 2006;354(20):2142–50.
110. Talukdar R, Vege SS. Recent developments in acute pancreatitis. Clin Gastroenterol Hepatol. 2009;7(11 Suppl):S3–9.
111. Koo BC, Chinogureyi A, Shaw AS. Imaging acute pancreatitis. Br J Radiol. 2010;83(986):104–12.
112. Mao L, Qiu Y. The classification of acute pancreatitis: current status. Intractable Rare Dis Res. 2012;1(3):134–7.
113. Papachristou GI, Muddana V, Yadav D, O'Connell M, Sanders MK, Slivka A, et al. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. Am J Gastroenterol 2010;105(2):435–41; quiz 42.
114. Ranson JH, Rifkind KM, Turner JW. Prognostic signs and nonoperative peritoneal lavage in acute pancreatitis. Surg Gynecol Obstet. 1976;143(2):209–19.
115. Wilson C, Heath DI, Imrie CW. Prediction of outcome in acute pancreatitis: a comparative study of APACHE II, clinical assessment and multiple factor scoring systems. Br J Surg. 1990;77(11):1260–4.
116. Pezzilli R, Zerbi A, Di Carlo V, Bassi C, Delle Fave GF, Working Group of the Italian Association for the Study of the Pancreas on Acute P. Practical guidelines for acute pancreatitis. Pancreatology. 2010;10(5):523–35.
117. Tenner S, Baillie J, DeWitt J, Vege SS, American College of G. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108(9):1400–15.
118. Bai Y, Gao J, Zou DW, Li ZS. Prophylactic antibiotics cannot reduce infected pancreatic necrosis and mortality in acute necrotizing pancreatitis: evidence from a meta-analysis of randomized controlled trials. Am J Gastroenterol. 2008;103(1):104–10.
119. Jafri NS, Mahid SS, Idstein SR, Hornung CA, Galandiuk S. Antibiotic prophylaxis is not protective in severe acute pancreatitis: a systematic review and meta-analysis. Am J Surg. 2009;197(6):806–13.
120. Wittau M, Mayer B, Scheele J, Henne-Bruns D, Dellinger EP, Isenmann R. Systematic review and meta-analysis of antibiotic prophylaxis in severe acute pancreatitis. Scand J Gastroenterol. 2011;46(3):261–70.
121. Ito K, Ito H, Whang EE. Timing of cholecystectomy for biliary pancreatitis: do the data support current guidelines? J Gastrointest Surg. 2008;12(12):2164–70.
122. Aboulian A, Chan T, Yaghoubian A, Kaji AH, Putnam B, Neville A, et al. Early cholecystectomy safely decreases hospital stay in patients with mild gallstone pancreatitis: a randomized prospective study. Ann Surg. 2010;251(4):615–9.
123. Hui CK, Lai KC, Yuen MF, Wong WM, Chan AO, Ng M, et al. The role of cholecystectomy in reducing recurrent gallstone pancreatitis. Endoscopy. 2004;36(3):206–11.
124. van Geenen EJ, van der Peet DL, Mulder CJ, Cuesta MA, Bruno MJ. Recurrent acute biliary pancreatitis: the protective role of cholecystectomy and endoscopic sphincterotomy. Surg Endosc. 2009;23(5):950–6.
125. Trust MD, Sheffield KM, Boyd CA, Benarroch-Gampel J, Zhang D, Townsend Jr CM, et al. Gallstone pancreatitis in older patients: are we operating enough? Surgery. 2011;150(3):515–25.
126. Halabi WJ, Kang CY, Ketana N, Lafaro KJ, Nguyen VQ, Stamos MJ, et al. Surgery for gallstone ileus: a nationwide comparison of trends and outcomes. Ann Surg. 2014;259(2):329–35.
127. Clavien PA, Richon J, Burgan S, Rohner A. Gallstone ileus. Br J Surg. 1990;77(7):737–42.
128. Ayantunde AA, Agrawal A. Gallstone ileus: diagnosis and management. World J Surg. 2007;31(6):1292–7.
129. Ravikumar R, Williams JG. The operative management of gallstone ileus. Ann R Coll Surg Engl. 2010;92(4):279–81.
130. Yu CY, Lin CC, Shyu RY, Hsieh CB, Wu HS, Tyan YS, et al. Value of CT in the diagnosis and management of gallstone ileus. World J Gastroenterol. 2005;11(14):2142–7.
131. Reisner RM, Cohen JR. Gallstone ileus: a review of 1001 reported cases. Am Surg. 1994;60(6):441–6.
132. Huffman JL, Schenker S. Acute acalculous cholecystitis: a review. Clin Gastroenterol Hepatol. 2010;8(1):15–22.
133. Barie PS, Eachempati SR. Acute acalculous cholecystitis. Gastroenterol Clin N Am 2010;39(2):343–57, x.
134. Simorov A, Ranade A, Parcells J, Shaligram A, Shostrom V, Boilesen E, et al. Emergent cholecystostomy is superior to open cholecystectomy in extremely ill patients with acalculous cholecystitis: a large multicenter outcome study. Am J Surg 2013;206(6):935–40; discussion 40–1.
135. Drossman DA, Dumitrascu DL. Rome III: new standard for functional gastrointestinal disorders. J Gastrointestin Liver Dis. 2006;15(3):237–41.
136. Mahid SS, Jafri NS, Brangers BC, Minor KS, Hornung CA, Galandiuk S. Meta-analysis of cholecystectomy in symptomatic patients with positive hepatobiliary iminodiacetic acid scan results without gallstones. Arch Surg. 2009;144(2):180–7.
137. Baillie J. Sphincter of Oddi dysfunction. Curr Gastroenterol Rep. 2010;12(2):130–4.

138. Canlas KR, Branch MS. Role of endoscopic retrograde cholangiopancreatography in acute pancreatitis. World J Gastroenterol. 2007;13(47):6314–20.
139. Sabbaghian MS, Rich BS, Rothberger GD, Cohen J, Batash S, Kramer E, et al. Evaluation of surgical outcomes and gallbladder characteristics in patients with biliary dyskinesia. J Gastrointest Surg. 2008;12(8):1324–30.
140. Skipper K, Sligh S, Dunn E, Schwartz A. Laparoscopic cholecystectomy for an abnormal hepato-iminodiacetic acid scan: a worthwhile procedure. Am Surg. 2000;66(1):30–2.
141. Geenen JE, Hogan WJ, Dodds WJ, Toouli J, Venu RP. The efficacy of endoscopic sphincterotomy after cholecystectomy in patients with sphincter-of-Oddi dysfunction. N Engl J Med. 1989;320(2):82–7.
142. Behar J, Corazziari E, Guelrud M, Hogan W, Sherman S, Toouli J. Functional gallbladder and sphincter of oddi disorders. Gastroenterology. 2006;130(5):1498–509.
143. Morgan KA, Romagnuolo J, Adams DB. Transduodenal sphincteroplasty in the management of sphincter of Oddi dysfunction and pancreas divisum in the modern era. J Am Coll Surg 2008;206(5):908–14; discussion 14–7.
144. Ash-Miles J, Roach H, Virjee J, Callaway M. More than just stones: a pictorial review of common and less common gallbladder pathologies. Curr Probl Diagn Radiol. 2008;37(5):189–202.
145. Ito H, Hann LE, D'Angelica M, Allen P, Fong Y, Dematteo RP, et al. Polypoid lesions of the gallbladder: diagnosis and followup. J Am Coll Surg. 2009;208(4):570–5.
146. Gallahan WC, Conway JD. Diagnosis and management of gallbladder polyps. Gastroenterol Clin N Am 2010;39(2):359–67, x.
147. Pilgrim CH, Groeschl RT, Pappas SG, Gamblin TC. An often overlooked diagnosis: imaging features of gallbladder cancer. J Am Coll Surg. 2013;216(2):333–9.
148. Colecchia A, Larocca A, Scaioli E, Bacchi-Reggiani ML, Di Biase AR, Azzaroli F, et al. Natural history of small gallbladder polyps is benign: evidence from a clinical and pathogenetic study. Am J Gastroenterol. 2009;104(3):624–9.
149. Koga A, Watanabe K, Fukuyama T, Takiguchi S, Nakayama F. Diagnosis and operative indications for polypoid lesions of the gallbladder. Arch Surg. 1988;123(1):26–9.
150. Zielinski MD, Atwell TD, Davis PW, Kendrick ML, Que FG. Comparison of surgically resected polypoid lesions of the gallbladder to their pre-operative ultrasound characteristics. J Gastrointest Surg. 2009;13(1):19–25.
151. Donald G, Sunjaya D, Donahue T, Hines OJ. Polyp on ultrasound: now what? The association between gallbladder polyps and cancer. Am Surg. 2013;79(10):1005–8.
152. Kwon W, Jang JY, Lee SE, Hwang DW, Kim SW. Clinicopathologic features of polypoid lesions of the gallbladder and risk factors of gallbladder cancer. J Korean Med Sci. 2009;24(3):481–7.
153. Yang HL, Sun YG, Wang Z. Polypoid lesions of the gallbladder: diagnosis and indications for surgery. Br J Surg. 1992;79(3):227–9.
154. Choi WB, Lee SK, Kim MH, Seo DW, Kim HJ, Kim DI, et al. A new strategy to predict the neoplastic polyps of the gallbladder based on a scoring system using EUS. Gastrointest Endosc. 2000;52(3):372–9.
155. Mishra G, Conway JD. Endoscopic ultrasound in the evaluation of radiologic abnormalities of the liver and biliary tree. Curr Gastroenterol Rep. 2009;11(2):150–4.
156. Kubota K, Bandai Y, Noie T, Ishizaki Y, Teruya M, Makuuchi M. How should polypoid lesions of the gallbladder be treated in the era of laparoscopic cholecystectomy? Surgery. 1995;117(5):481–7.
157. Lee KF, Wong J, Li JC, Lai PB. Polypoid lesions of the gallbladder. Am J Surg. 2004;188(2):186–90.
158. Park JY, Hong SP, Kim YJ, Kim HJ, Kim HM, Cho JH, et al. Long-term follow up of gallbladder polyps. J Gastroenterol Hepatol. 2009;24(2):219–22.
159. Sicklick JK, Choti MA. Controversies in the surgical management of cholangiocarcinoma and gallbladder cancer. Semin Oncol. 2005;32(6 Suppl 9):S112–7.
160. Eslick GD. Epidemiology of gallbladder cancer. Gastroenterol Clin N Am 2010;39(2):307–30, ix.
161. Mastoraki A, Papanikolaou IS, Konstandiadou I, Sakorafas G, Safioleas M. Facing the challenge of treating gallbladder carcinoma. Review of the literature. Hepatogastroenterology. 2010;57(98):215–9.
162. Ramos-Font C, Gomez-Rio M, Rodriguez-Fernandez A, Jimenez-Heffernan A, Sanchez Sanchez R, Llamas-Elvira JM. Ability of FDG-PET/CT in the detection of gallbladder cancer. J Surg Oncol. 2014;109(3):218–24.
163. Jayaraman S, Jarnagin WR. Management of gallbladder cancer. Gastroenterol Clin N Am 2010;39(2):331–42, x.
164. Weber SM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR. Staging laparoscopy in patients with extrahepatic biliary carcinoma. Analysis of 100 patients. Ann Surg. 2002;235(3):392–9.
165. Maker AV, Butte JM, Oxenberg J, Kuk D, Gonen M, Fong Y, et al. Is port site resection necessary in the surgical management of gallbladder cancer? Ann Surg Oncol. 2012;19(2):409–17.
166. Hyder O, Dodson RM, Sachs T, Weiss M, Mayo SC, Choti MA, et al. Impact of adjuvant external beam radiotherapy on survival in surgically resected gallbladder adenocarcinoma: a propensity score-matched Surveillance, Epidemiology, and End Results analysis. Surgery. 2014;155(1):85–93.