Managing Gallstone Disease in the Elderly

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KEYWORDS

• Gallstone disease • Cholecystitis • Choledocholithiasis • Elderly
• Geriatric population

KEY POINTS

- Geriatric patients tend to have subtle presentations of biliary disorders and, if untreated, can decompensate acutely.
- Acute cholecystitis, a common complication of gallstones, is treated by conservative measures and cholecystectomy, laparoscopic or open, among patients with optimal surgical risk. High-risk patients undergo temporizing interventions, percutaneous or endoscopic, enabling definitive therapy. Acute cholecystitis with complications, including perforations, gangrene, and small bowel obstruction, warrants emergent cholecystectomy.
- Migration of gallstones into the biliary system can cause choledocholithiasis, which commonly results in complications, including biliary pancreatitis or cholangitis if not intervened. Therapy for common bile duct calculi is based on biliary clearance through endoscopic and, less commonly, surgical approaches.

INTRODUCTION

Gallstone disease is widely prevalent among the United States population and has been estimated to affect about 20 million people.[1] It is a leading cause of inpatient hospitalization in the United States and costs more than $6 billion annually.[2,3] Among the elderly population, the overall prevalence of gallstone disease ranges from 14% to 23% and can approach up to 80% for individuals more than 90 years old.[4] Advanced age has been considered an independent risk factor for incidence of gallstones. The prolongation of life expectancy is expected to alter patient demographics, causing more individuals with advanced age and, subsequently, an incremental increase in gallstone burden.

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With progression of age, the biliary tract undergoes anatomic and physiologic changes[5–8] (Fig. 1). Geriatric patients tend to have subtle presentation of biliary disorders and can decompensate acutely if untreated.[9] They have higher rates of complications and slower recovery because of delayed healing, comorbidities, and weaker immune systems. The management of gallstones must incorporate therapeutic goals ranging from improvement of quality of life and maintenance of independence to absolute cure.[10] This article reviews the management of gallstone disease involving both the gallbladder and associated ductal system among the elderly.

ASYMPTOMATIC CHOLELITHIASIS

Gallstones are asymptomatic in most individuals and incidentally diagnosed through imaging. A recent study by Shabanzadeh and colleagues[11] included 664 patients with gallstones with a median age of 60 years, among whom 19.6% of participants developed gallstone-related events (8.0% complicated and 11.6% uncomplicated). The study showed a negative association between age and gallstone-related events. Similar trends have been observed in prior cohort studies.[12,13]

Management

Prophylactic surgery

No prospective trial has been performed to establish the efficacy of surgical or medical therapy among asymptomatic gallstone carriers. In a decision-analysis study, prophylactic surgery had a negative survival impact.[14] Its role is limited to individuals with primary risk factors of gallbladder cancer.[15]

Expectant management

Although consensus is lacking, observation and annual follow-up of asymptomatic gallstones have been suggested by some guidelines.[16]

Medical therapy

Gallstones with smaller sizes (<10 mm) and lower calcium concentrations (radiolucent stones) are amenable to therapy by ursodeoxycholic acid. They act by inhibiting

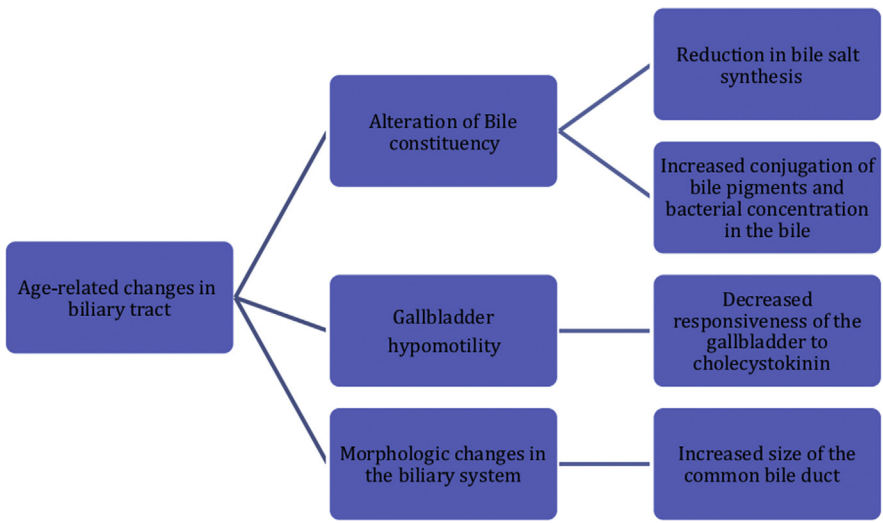

Fig. 1. Age-related changes within the biliary system.

intestinal cholesterol absorption and subsequent fragmentation and expulsion of stones and can be used for primary prophylaxis for gallstones.[17,18]

BILIARY COLIC

Gallbladder contraction against the cystic duct opening may cause right upper quadrant or epigastric pain of variable severity, associated with postprandial exacerbations and nocturnal variations.[19–21] Elderly patients may present with altered mental status, falls, or incontinence.[22]

Among symptomatic patients, gallstones are commonly diagnosed through ultrasonography (US) and appear as acoustic shadows (**Fig. 2**A, B). Biliary sludge observed on US may indicate microlithiasis and has resulted in complications warranting cholecystectomy.[23] Despite omission of small stones or sludge, US has a diagnostic sensitivity and specificity of 84% (95% confidence interval [CI], 0.76–0.92) and 99% (95% CI, 0.97–1.00) respectively.[24]

Treatment

Elective cholecystectomy

Natural history studies have shown occurrence of complications among untreated symptomatic gallstones.[25] Elderly patients with symptomatic gallstones must be considered for an elective cholecystectomy based on their surgical risk. A minimally invasive approach is preferred except in patients with gallbladder architectural distortion or associated gallbladder cancer risks.[26] Postponing cholecystectomy may cause accumulation of comorbidities with age and a higher surgical risk. Furthermore, late presentations and complications may warrant emergent cholecystectomy, which is associated with worse outcomes and has associated mortality of 6% to 15%.[27,28]

Medical resolution therapy

Reduction in biliary pain and risk of cholecystitis have been shown among patients with biliary colic with medical therapy, including bile acid therapy and extracorporeal shock wave lithotripsy.[29] A meta-analysis showed a 37% dissolution rate among individuals with gallstones.[30] However, medical therapy should be reserved for patients who refuse or are unfit for surgery.

ACUTE CHOLECYSTITIS

Acute cholecystitis refers to acute inflammation of the gallbladder, which in most cases results from gallstones, except among 5% to 10% of patients with acalculous

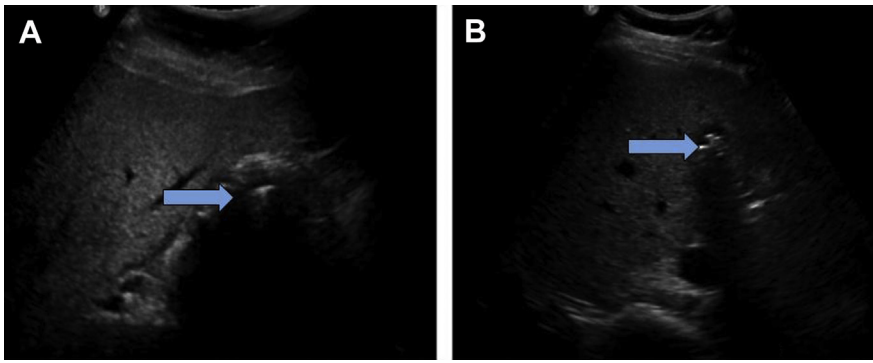

Fig. 2. (*A*) Sagittal and (*B*) axial views of a stone in 75-year-old woman with biliary colic. The arrow points to the stone.

cholecystitis. Acute calculous cholecystitis results from cystic duct obstruction and increased intraluminal pressure and congestion. In addition, lysolecithin, an enzyme arising from mucosal irritation by gallstones, causes gallbladder inflammation.[31,32] Superimposed infections may also contribute, as shown among patients with gallstones with positive cultures found in 22% to 46% of bile samples from the gallbladder and common bile duct (CBD).[33]

Clinical Presentation

Patients with acute cholecystitis generally present with right upper quadrant or epigastric pain. Proximity to the parietal peritoneum may cause local inflammation, guarding, and a positive Murphy sign. However, among the geriatric population, the symptoms are atypical and physical signs may be masked by neuropathy. The Murphy sign has a lower sensitivity of 48% among the elderly, compared with 65% among the general population.[34,35]

Diagnostic Approach

Laboratory findings

Typical leukocytosis and bandemia may be obscured among the elderly; thus, a higher index of clinical suspicion is imperative. Marked increases in bilirubin level and liver chemistry are seldom observed and often indicate complications such as cholangitis, choledocholithiasis, or Mirizzi syndrome (an extrinsic compression of CBD by the neck of the gallbladder).

Imaging modality

1. US is the most common imaging modality for the diagnosis of acute cholecystitis. A systematic review suggested the adjusted sensitivity and specificity for sonographic diagnosis of acute cholecystitis to be 88% and 80% respectively. The features on US that support acute cholecystitis include gallbladder wall thickening, pericholecystic fluid, and sonographic Murphy sign.[24]
2. Cross-sectional imaging is rarely used for diagnosis of acute cholecystitis, except for detection of its complications or ruling out alternate differentials (**Fig. 3**A–C).
3. Cholescintigraphy (99mTc-heaptoiminodiacetic acid [HIDA] scanning) is used for diagnosis of acute cholecystitis among individuals with negative US results. A large study compared HIDA scan with abdominal US among patients with acute cholecystitis and revealed significantly higher sensitivity (90.7% vs 64.0%, $P<.001$) and specificity (71.4% vs 58.4%, $P = .005$).[36]

Complications

Gangrenous cholecystitis

Gangrenous cholecystitis (GC) is the most common complication of acute cholecystitis. Prevalent in around 20% of patients with acute cholecystitis, GC results from transmural inflammation and gallbladder ischemia. It occurs particularly among individuals with a prolonged course and those with vasculopathy.[37] Radiologically, GC is diagnosed through computed tomography (CT) findings of the gallbladder and is associated with gallbladder distention greater than 4.0 cm, mural striations, and decreased mural enhancement. GC warrants urgent cholecystectomy and is associated with higher rates of conversion from laparoscopic to open cholecystectomy. A cohort study showed significantly higher mortality (1%–2% vs 0.8%) and complication rates (10.8% vs 8.0%) among individuals with GC (n = 7017) compared with the entire cohort (n = 141,970).[38]

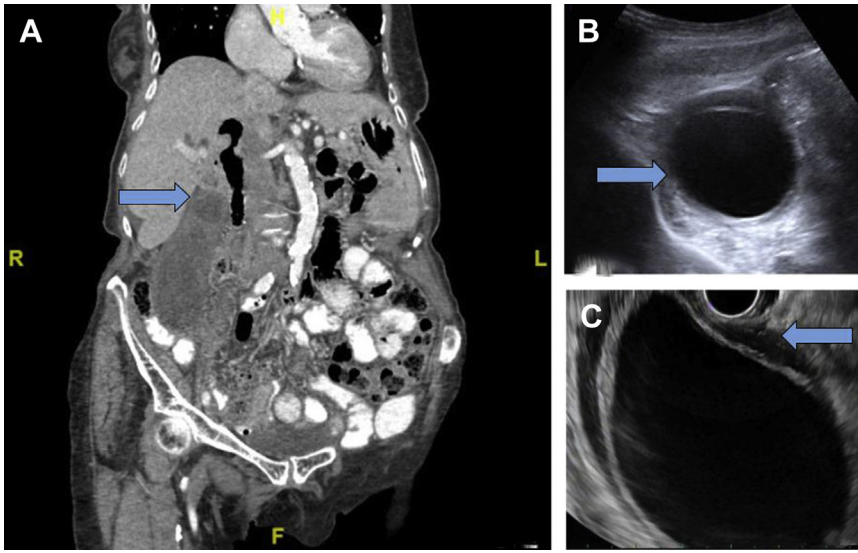

Fig. 3. (*A*) CT scan showing acute cholecystitis (*arrows*) in a 102-year-old woman. (*B*) US and (*C*) endoscopic US (EUS) visualization of acute cholecystitis including pericholecystic fluid.

Gallbladder perforation

Ongoing gallbladder inflammation from delayed diagnosis or failed therapy may result in gallbladder perforation. Gallbladder perforation is classified into 4 types based on the Niemeier classification and its modification: type 1, free perforation; type 2, perforation with abscess; type 3, chronic perforation with cholecystoenteric fistula; or type 4, perforation into biliary tree resulting in formation of cholecystobiliary fistulae.[39,40]

Emphysematous cholecystitis

Emphysematous cholecystitis (EC), a fulminant complication of acute cholecystitis, is characterized by accumulation of gas within the gallbladder wall or lumen or its biliary duct extension. It is caused by secondary infection by gas-forming organisms such as *Clostridium welchii*. EC commonly occurs in the setting of gallbladder ischemia, and among individuals with advanced age, diabetes, or nephropathy. On US, detection of air within the gallbladder wall has high specificity but may obscure visualization of the gallbladder. CT imaging is accurate in the diagnosis of gas within the gallbladder wall and surrounding structures and enables gradation based on the extent of spread. EC is managed by emergent cholecystectomy. Open cholecystectomy is preferred for patients with peritoneal involvement.

Cholecystoenteric fistula

Cholecystoenteric fistula occurs because of pressure necrosis from long-standing gallbladder stones and perforation of the gallbladder wall into the intestinal lumen. Cholecystoenteric fistula presents as bilious diarrhea or, rarely, may result in gallstone ileus.

Gallstone ileus

Gallstone ileus is defined as small bowel obstruction caused by impacted gallstones, which are generally 2 to 2.5 cm in size. Gallstone ileus is commonly found among frail elderly individuals (average age of incidence, 74 years) and is found in up to 25% of elderly individuals with small bowel obstruction.[41,42] It is classically associated with

the Rigler triad: pneumobilia, small bowel obstruction, and ectopic radio-opaque gallstones, which is incident in about 15% of the cases.[43] CT scan of the abdomen has variable sensitivity in diagnosing gallstones but has high diagnostic sensitivity for bowel obstruction.[44] Besides management for obstruction, gallstone ileus is treated surgically by enterolithotomy, with or without cholecystectomy.[42,45]

Treatment of Acute Cholecystitis

Supportive care

Patients with acute calculous cholecystitis require inpatient care with supportive measures such as intravenous hydration and analgesia through nonsteroidal antiinflammatory drugs (NSAIDs). Opioids increase sphincter of Oddi pressure and are used when NSAIDs have inadequate response or are contraindicated.[46] Antibiotics are indicated for acute cholecystitis with complications or among frail and immunocompromised individuals.[47] They prevent septic complications before surgery and can be discontinued 24 hours after gallbladder removal or clinical resolution.

Risk stratification

Patients with acute cholecystitis warrant definitive therapy. Although cholecystectomy is the gold standard, patients must undergo risk stratification to determine the choice of therapy. The following systems facilitate guidance for surgical candidacy of patients with acute cholecystitis:

- Tokyo Guidelines 2018: grade I to III cholecystitis.[48]
- American Association of Surgery of Trauma (AAST) System: grade I to V cholecystitis.[49]
- Parkland Grading Scale for Cholecystitis: based on the intraoperative appearance of the gallbladder.[50]
- American Society of Anesthesiologists (ASA): patients with low-risk (ASA I/II) or high-risk (ASA III–V) cholecystitis.

Cholecystectomy

Cholecystectomy is the preferred procedure for patients with acute cholecystitis with low surgical risk.[51]

Methods of surgery

- Laparoscopic cholecystectomy: this approach has become the standard modality for surgical resection among elderly patients with mild to moderate acute cholecystitis.[52] It has better perioperative survival and fewer complications, including wound infections and pneumonia.[53] However, patients with acute cholecystitis have higher technical requirements because of acute inflammation, causing adhesions and altered anatomy.

  Acute cholecystitis may also cause so-called difficult gallbladder, a term for cholecystectomy procedures with increased procedural risk from bleeding (eg, liver cirrhosis) or anatomic distortion.[54] Difficult dissection should prompt surgeons to choose a fundus-first approach, subtotal cholecystectomy, or conversion into open cholecystectomy.[55,56]
- Open cholecystectomy: although associated with higher local complications, an open approach enables more vascular and duct control. It must be attempted for patients with porcelain gallbladder and contraindications to pneumoperitoneum.
- Natural orifice transluminal endoscopic surgery (NOTES): this procedure has a limited role in acute cholecystitis because of altered surgical anatomy and higher dissection requirements. The procedure involves gallbladder access through

natural orifices, including transvaginal or transgastric approach. It has been attempted in limited medical centers and promises faster recovery and better cosmetic outcomes.[57,58]

Timing of surgery

Current evidence favors early cholecystectomy (0–3 days) rather than delayed cholecystectomy among surgically fit individuals.[59,60] A recent meta-analysis of studies of early cholecystectomy among the geriatric population reports perioperative morbidity of 24% and mortality of 3.5%.[61]

Safety

1. Morbidity and mortality: elderly individuals tend to have higher ASA grades and comorbidity burden (assessed through the Charlson Comorbidity Index). In a recent systematic review, a significantly higher morbidity rate was observed among the geriatric population compared with younger individuals. No significant difference in intraoperative complications was observed; however, lower conversion rates were observed among younger individuals (relative risk, 0.96; 0.94–0.98).[62]
2. Biliary and vascular injury: higher rates of biliary injury were noted among elderly patients undergoing gallbladder surgery. In a cross-sectional analysis based on the National Inpatient Survey, the rate of bile duct injury among individuals aged less than 50 years was 0.10%, 60 to 79 years was 0.13%, and greater than or equal to 80 years was 0.14% ($P<.003$).[63] Laparoscopic cholecystectomy is associated with higher rates of bile duct injury compared with open cholecystectomy.[64,65] During surgical procedures, a critical view of safety should be performed in order to prevent biliary and vascular injury during cholecystectomy.[66,67]

Emergency cholecystectomy

In addition to supportive measures, emergent cholecystectomy is indicated for acute cholecystitis with complications. It is also indicated in patients with acute cholecystitis with hemodynamic instability and sepsis.

Percutaneous cholecystostomy

Patients with acute cholecystitis with increased surgical risk who are septic or critically ill, and those lacking clinical response to antibiotics with greater than 72 hours of symptom onset, warrant gallbladder drainage through percutaneous cholecystostomy.[68,69] The procedure can be performed through transperitoneal or transhepatic routes and has a technical success rate of around 85%.[70] Although transhepatic approach is preferred because of its better safety profile, it is challenging among individuals with cirrhosis. It is contraindicated among individuals with coagulopathy and can be complicated by vascular injury, biliary leak, peritonitis, and catheter dislodgement.[71] High-quality evidence supporting its use as a definitive drainage procedure is lacking. Recent evidence shows higher complication rates, disease recurrence, reintervention, and median hospital stay among individuals undergoing percutaneous interventions.[72,73]

Endoscopic gallbladder drainage

Endoscopic techniques can be used as a bridge to surgery or destination therapy among high-risk patients, especially those with coagulopathy and suboptimal anatomy, including inaccessible gallbladder, ascites, and advanced cirrhosis.[74] Endoscopic gallbladder drainage is attempted through transpapillary or transmural approaches.

- Endoscopic transpapillary gallbladder drainage involves passage of a drainage catheter through the cystic duct under fluoroscopic guidance to access the gallbladder. The other end of the catheter is passed through the nose or drains into the duodenum. This technique is limited by tortuosity of the cystic duct and dependence on fluoroscopic visualization. Its pooled technical success rate has been estimated to be 80% to 91%.[75,76]
- Endoscopic US (EUS)–guided transmural gallbladder drainage (GBD) enables access to the gallbladder through the transgastric or transduodenal passage of a needle and placement of either a drain or stent. Self-expanding stents have now been replaced by lumen-apposing metallic stents (LAMSs) (**Fig. 4**A–F). They provide reliable anchorage because of double-walled flanges perpendicular to the lumen and have lesser complications. The technical success of EUS-GBD via LAMS has been observed to be as high as 95.2%.[77] Compared with percutaneous interventions, EUS-GBD showed fewer adverse events (odds ratio [OR], 0.43; 95% CI, 0.18–1.00), shorter hospitalizations (2.53 days; 95% CI, −4.28 to −0.78), and fewer reinterventions (OR, 0.16; 95% CI, 0.04–0.042) and readmissions (OR, 0.16; 95% CI, 0.05–0.53).[78] Significantly better clinical success and safety have been observed in EUS-guided drainage vis-à-vis transpapillary drainage.[79]

Post–gallbladder drainage care

Clinical resolution after a percutaneous or endoscopic procedure warrants risk stratification. Low-risk patients can be considered for elective cholecystectomy.[80,81] Individuals with high surgical risk have the following options:

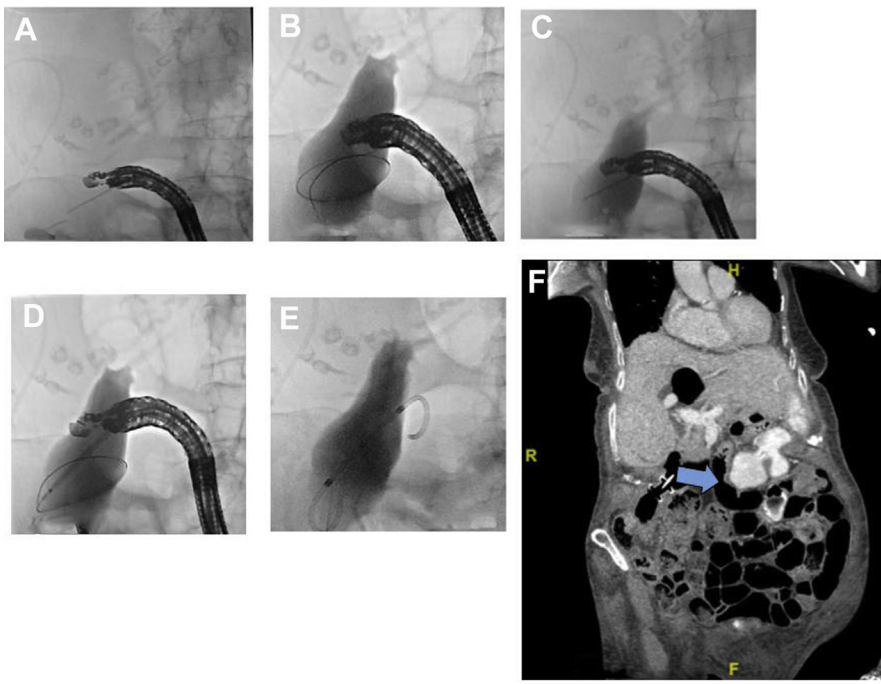

Fig. 4. (*A–E*) Steps of EUS-guided LAMS placement in a patient with acute cholecystitis. (*F*) CT image of a patient after LAMS placement. *Arrow* denotes GB Drainage through LAMS.

- Clinical decompensation at any time warrants emergent cholecystectomy.
- Expectant management and interval cholecystectomy: one of the approaches for patients with high surgical risk is to follow them and attempt cholecystectomy only among those with recurrent acute cholecystitis.[82]
- Percutaneous stone extraction: after maturation of cholecystostomy tract (2–3 weeks after percutaneous drainage), dilation through graded dilators under fluoroscopic guidance and stone extraction is performed.[83,84]
- Extracorporeal lithotripsy: this procedure involves passage of shockwaves and enables breaking the stones in the gallbladder and their passage through biliary system.
- Endoscopic gallstone extraction: endoscopic removal of gallstones has been successfully shown through the use of LAMSs.[85]

CHRONIC CHOLECYSTITIS

Long-standing gallstones or prior episodes of acute cholecystitis may cause indolent gallbladder inflammation, also called chronic cholecystitis. On histology, gallbladder wall thickening, serosal adhesions, smooth muscle hypertrophy, and pathognomonic Rokitansky-Aschoff sinuses are observed.[86] The chronic inflammation may cause gallbladder calcification and porcelain gallbladder, the mechanism of which is unclear.[87]

Clinical Presentation

These patients generally present with insidious biliary colic, which may progress over the chronic course. Older individuals may have an uncomfortable feeling or loss of appetite prompting clinical evaluation.

Diagnosis

US is a noninvasive diagnostic modality that may reveal a thickened gallbladder wall or shrunken fibrotic gallbladder with gallstones. HIDA scan can also be used for confirmation of the diagnosis.

Treatment

Conservative therapy

For biliary colic, NSAIDs are preferred as analgesics. Antibiotics should be started in patients who have evidence of sepsis.

Definitive therapy

Cholecystectomy is considered when the acute symptoms have subsided. Chronic cholecystitis can be treated by cholecystectomy, through a laparoscopic or open approach. Laparoscopic cholecystectomy has lower complication rates and faster recovery. An open approach should be used on suspicion of gallbladder cancer.[88] Altered surgical anatomy caused by prior surgeries or adhesions also supports open methods.[89]

Expectant management

Patients with high surgical risk may also be managed conservatively through dietary restriction and medical resolution therapy.

CHOLEDOCHOLITHIASIS

Choledocholithiasis refers to the presence of gallstones in the CBD. Although associated with up to 5% to 20% of patients with gallstones, the exact incidence and

prevalence of choledocholithiasis is unknown.[90] Among the elderly, most calculi originate from the gallbladder and migrate into the CBD.[91] Alternatively, primary choledocholithiasis may result from long-standing biliary stasis associated with conditions including CBD dilatation and periampullary diverticulum (PAD).[92]

Asymptomatic Choledocholithiasis

Asymptomatic choledocholithiasis is diagnosed in up to half of patients with choledocholithiasis through abnormal laboratory values, radiologic findings, or intraoperative cholangiography (IOC) during cholecystectomy.[93]

Risk of progression

Because of the paucity of studies investigating the natural history of asymptomatic choledocholithiasis, the risk of progression to symptomatic and complicated CBD stones remains elusive. A study of patients undergoing laparoscopic cholecystectomy with IOC and delayed postoperative cholangiography revealed persistence of CBD calculi in only about 50% of individuals.[94–96]

In contrast, a study on Swedish Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks) reported unfavorable outcomes in 25.3% of the individuals with choledocholithiasis who did not undergo any intervention.[97] A significantly lower risk was observed among patients in whom any measures for biliary ductal clearance were taken (12.7%; OR, 0.44 [0.35–0.55]).

Symptomatic Choledocholithiasis

Patients with choledocholithiasis may be asymptomatic, have epigastric or right upper quadrant pain, or present with complications including cholangitis or biliary pancreatitis.

Complications of Choledocholithiasis

Acute cholangitis

Acute cholangitis results from CBD inflammation caused by biliary stasis and superimposed infection, most probably from gram-negative bacteria.[98,99] Presentation of cholangitis among the geriatric population is atypical and lacks correlation with severity.[100] The diagnostic criteria for cholangitis include evidence of systemic inflammation, cholestasis, and imaging (**Box 1**).[101]

The imaging modalities for evaluation of cholangitis include US and, if negative, CT scan for detection of biliary dilatation or evidence of underlying obstructive cause. In case of diagnostic dilemma, MRI/magnetic resonance cholangiopancreatography (MRCP) and EUS can also be used[102] (**Figs. 5**A, B and **6**).

Old age is an important risk factor for mortality among patients with acute cholangitis.[103] Among the elderly, acute cholangitis is associated with delayed medical care from masked presentation and significantly higher rates of hypotension, peritonism, renal failure.[104]

The assessment for severity is based on concomitant organ dysfunction, as described in **Box 2**.[101]

Acute biliary pancreatitis

Among the elderly, age-related biliary dilatation and incremental incidence of gallstones result in predominance of a biliary cause of acute pancreatitis. Age is an independent criterion for severity scoring systems of acute pancreatitis, including the Glasgow scoring system, Ranson scoring system, and Acute Physiology and Chronic Health Evaluation (APACHE II).[105–107] Among geriatric patients, higher comorbidity burden is associated with mortality from acute pancreatitis.[108] Acute biliary

Box 1
Diagnostic criteria for cholangitis

A. Systemic inflammation
   A1. Fever (>38°C) and/or shaking chills
   A2. Laboratory data. Evidence of inflammatory response: leukocytosis (<4000 or >10,000), increased C-reactive protein levels (≥1 mg/dL), and other changes indicating inflammation

B. Cholestasis
   B1. Jaundice (≥2 mg/dL)
   B2. Laboratory data: abnormal liver function tests (≥1.5 upper limit of normal)

C. Imaging:
   C1. Biliary dilatation
   C2. Evidence of the cause on imaging (eg, stricture, stone, stent)

Suspected diagnosis: 1 item in A plus 1 item in either B or C. Definite diagnosis: 1 item in A, 1 item in B, and 1 item in C.

pancreatitis (ABP) presents similarly to other causes of acute pancreatitis and is diagnosed by biochemical alteration of pancreatitis; namely, increased serum amylase/lipase level in the setting of gallstones.

Management of Choledocholithiasis

American Society for Gastrointestinal Endoscopy risk stratification

Risk stratification for choledocholithiasis has been proposed by the Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE).[109,110] The predictor for choledocholithiasis is based on biochemical and imaging parameters (summarized in **Box 3**).

Laboratory findings

Patients with choledocholithiasis tend to have a cholestatic pattern of liver tests. CBD dilatation and alteration of liver chemistry are moderate predictors in ASGE guidelines in preprocedural diagnosis of choledocholithiasis.[109,110] A meta-analysis of 22 studies revealed diagnostic sensitivity of 69% and a specificity of 88% for increased serum bilirubin level in the diagnosis of CBD stone.[111]

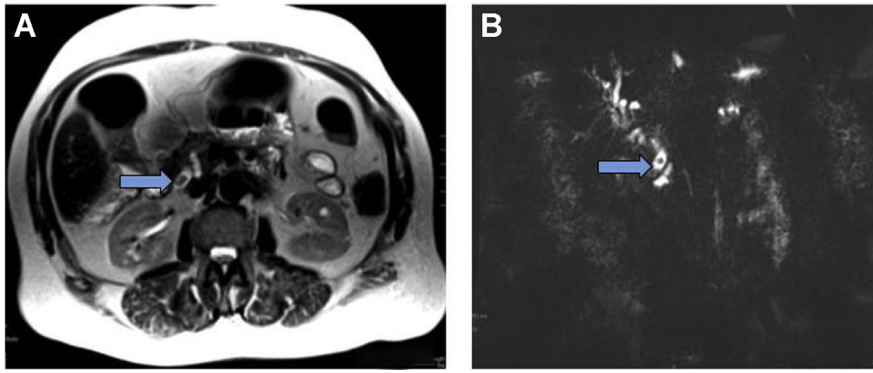

Fig. 5. CBD stone on (*A*) T2-MRI and (*B*) three-dimensional reconstruction images.

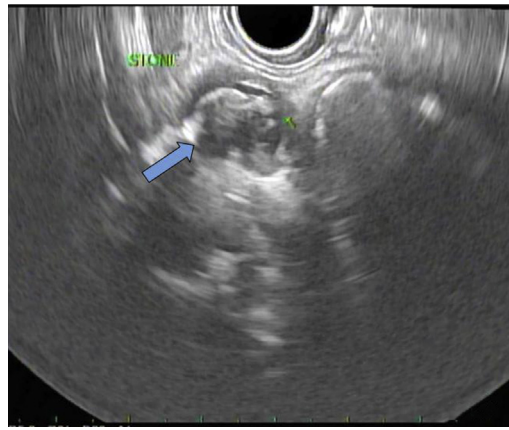

Fig. 6. CBD stone (*arrow*) on EUS.

Imaging

1. US: choledocholithiasis warrants initial work-up through transabdominal US. A meta-analysis investigated the diagnostic accuracy of liver enzymes and US for diagnosis of choledocholithiasis and showed pooled sensitivity of 73% (95% CI, 44%–95%) and specificity of 91% (95% CI, 84%–95%). Current ASGE guidelines include visualization of a stone or biliary duct dilatation on cross-sectional or sonographic imaging and total bilirubin level increase greater than4 mg/dL (strong predictors).[109,110] Although practice guidelines suggest 6 mm as a cutoff for choledocholithiasis, the CBD diameter varies with the patient's age.[112] A study by Bachar and colleagues[113] showed significantly greater CBD sizes among patients aged more than 50 years. This study revealed gradual ductal dilation of 0.04 mm/y and proposed an upper normal limit of 8.5 mm among the elderly. Nondilated CBD does not equate with no CBD stones, and each CBD dimension has an associated choledocholithiasis probability necessitating its application to overall clinical context.[114]

Box 2
Classification of severity of cholangitis

Grade III (severe) acute cholangitis: acute cholangitis in any of the following organs:
1. Cardiovascular: hypotension requiring dopamine greater than or equal to 5 μg/kg/min, or any dose of norepinephrine
2. Neurologic: altered consciousness
3. Respiratory: Pao_2/fraction of inspired oxygen less than 300
4. Renal: oliguria, serum creatinine level greater than 2.0 mg/dL
5. Hepatic: prothrombin time–International Normalized Ratio greater than 1.5
6. Hematological: platelet count less than 1 million/mm^3

Grade II (moderate) acute cholangitis associated with any 2 of the following:
1. Abnormal white blood cell count (>12,000/mm^3, <4000/mm^3)
2. High fever ($\geq$39°C)
3. Age ($\geq$75 years)
4. Hyperbilirubinemia (total bilirubin $\geq$5 mg/dL)
5. Hypoalbuminemia (<Upper limit of Normal Value $\times$ 0.7)

Grade I (mild): acute cholangitis not meeting the criteria for grade II/III acute cholangitis.

Box 3
American Society for Gastrointestinal Endoscopy risk criterion

Strong:
- CBD stones on transabdominal US
- Clinical ascending cholangitis
- Bilirubin level greater than 4 mg/dL and dilated CBD on US (>6 mm with gall bladder in situ and >8 mm after cholecystectomy)

Moderate
- Abnormal liver tests other than bilirubin
- Age>55 years
- Dilated CBD on US

Low
- Lack of intermediate and high risk factors

Adapted from ASGE Standards of Practice Committee, Buxbaum JL, Abbas Fehmi SM, et al. ASGE guideline on the role of endoscopy in the evaluation and management of choledocholithiasis. Gastrointest Endosc. 2019;89(6):1099; with permission.

2. Intraoperative cholangiography and intraoperative US: during cholecystectomy (open or laparoscopic), the bile duct system can be delineated through IOC. The procedure involves injection of water-soluble dye and subsequent radiologic visualization through fluoroscopy. Although its performance during surgeries is debated, anatomic characterization of the biliary tree by IOC can prevent biliary injury.[115] A systematic review showed higher summary sensitivity of 0.99 (95% CI, 0.83–1.00) versus 0.83(95% CI, 0.72–0.90) and specificity of 0.99 (95% CI, 0.95–1.00) versus 0.99 (95% CI, 0.94–1.00) for IOC compared with endoscopic retrograde cholangiopancreatography (ERCP).[116] In addition, intraoperative US (IUS) can be performed through insertion of the US probe into the peritoneal cavity. It has diagnostic sensitivity and specificity of 95% and 100%, reduces the need for IOC, and prevents bile duct injury.
3. EUS and MRCP: patients with intermediate risk should undergo EUS or MRCP. Although EUS can diagnose smaller stones (0.1 mm) compared with MRCP (1.5 mm), it is more invasive and associated with sedation and procedural risks (bleeding, perforations). Both modalities have high diagnostic sensitivity (EUS 0.95, 95% CI 0.91–0.97 versus MRCP 0.93, 95% CI 0.87–0.96) and specificity (EUS 0.97, 95% CI 0.94–0.99 versus MRCP 0.96, 95% CI 0.90–0.98) for choledocholithiasis.[117] The selection of these modalities is based on technical expertise, costs, availability, and sedation risks.
4. ERCP: among patients with suspected choledocholithiasis, ERCP can be used as a diagnostic and therapeutic modality. It is reserved for individuals with high likelihood of choledocholithiasis[118] (**Fig. 7**A–F).

Treatment

Uncomplicated choledocholithiasis is managed through CBD stone extraction via endoscopic or, in certain circumstances, surgical routes. Endoscopic and surgical CBD stone extraction have similar safety profiles, although the surgical approach is more invasive.[119] The technique of choice for CBD calculi extraction is based on institutional practice and availability of expertise.

Surgery Intraoperative CBD exploration through laparoscopic or open methods is commonly performed with cholecystectomy. The choice of surgical exploration is

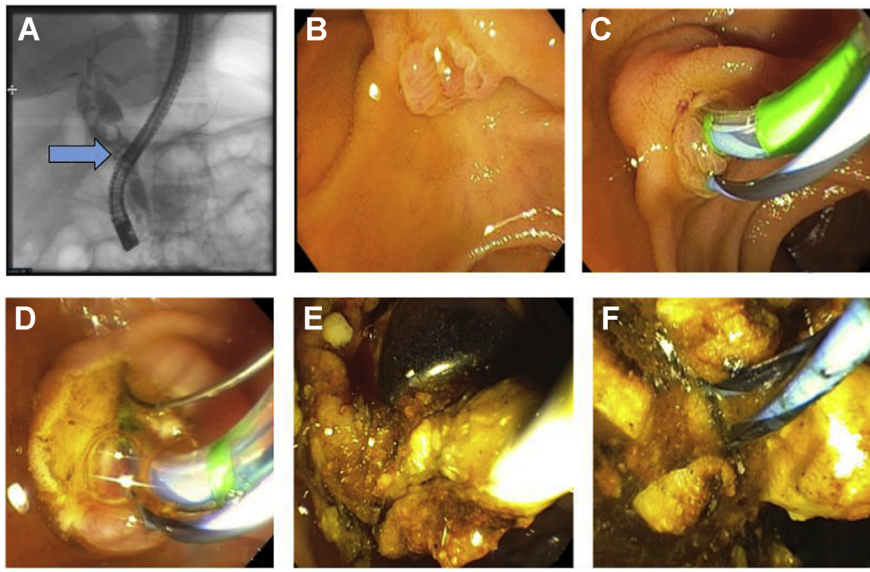

Fig. 7. (*A*) Fluoroscopic visualization of CBD stone. (*B–F*) CBD stone extraction through ERCP.

based on expertise and preference. Open CBD exploration has higher surgical morbidity, operative blood loss, and length of hospitalization.[120]

Endoscopic modality Patients with high risk for choledocholithiasis should be considered for ERCP for extraction of the calculi. Patients at moderate risk should undergo IOC/IUS, MRI, or EUS, followed by cholecystectomy (**Fig. 8**).

- ERCP technique involves deep cannulation of the bile duct via the major papilla, or, if cannulation is challenging, use of needle papillotome, called precut papillotomy.
- CBD stone clearance is attained through sphincterotomy (ie, incision through the deep muscle layer of the sphincter to maximize access to CBD stone) and/or balloon dilation and subsequent extraction through extraction balloons and baskets.
- For stones too large to remove en bloc, lithotripsy via mechanical baskets or cholangioscopic application of laser or electrohydraulic energy enables breaking down stones for removal (**Fig. 9**A–C).

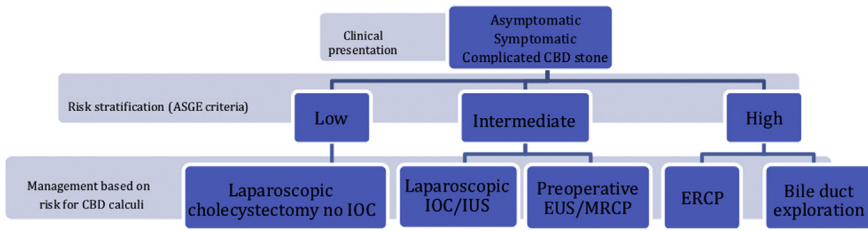

Fig. 8. Management of CBD calculi and related complications based on ASGE criteria.[110]

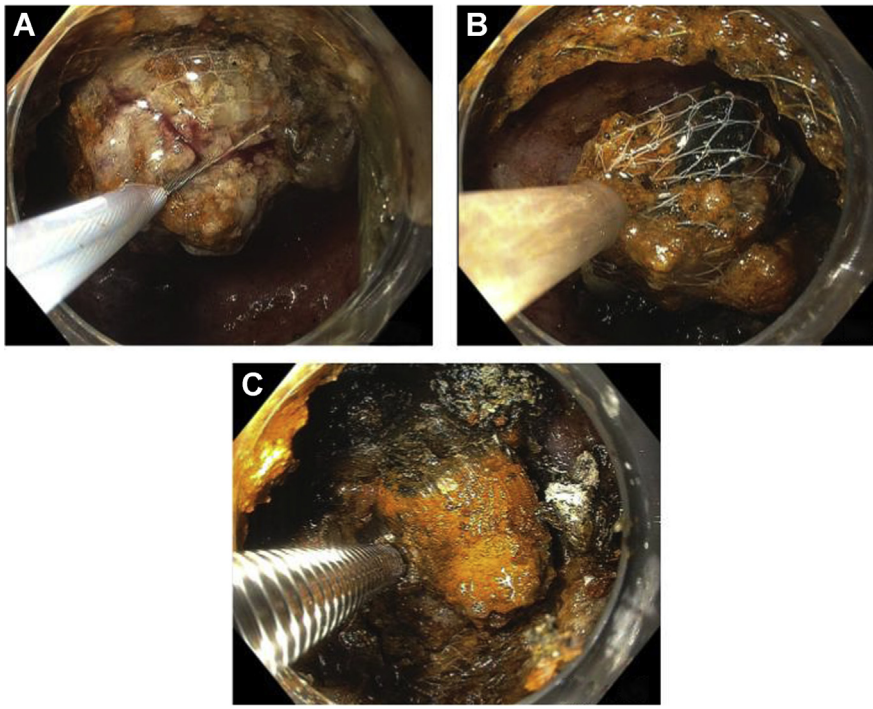

Fig. 9. (*A–C*) Endoscopic gallstone clearance via lithotripsy and stone extraction with Roth net through the LAMS.

Safety and outcomes of endoscopic retrograde cholangiopancreatography

Although performed routinely, ERCP has risks, which have been reported in up to 5% to 10% of cases. Their predisposing factors, outcomes, and preventive strategies are outlined in **Table 1**. Post-ERCP pancreatitis (PEP) is the most common complication of ERCP, although individuals aged greater than or equal to 65 years have a lower incidence than younger individuals.[121] The presence of choledocholithiasis is also protective against PEP, although the exact mechanism is not clear.[122] Age has been postulated as a protective factor for PEP. With advanced age, histologic alterations within the pancreatic parenchyma occur, including replacement of ductal epithelium with stratified squamous epithelium, fatty infiltration, and fibrosis.[123] Decreased perfusion, fibrosis, and atrophy may also cause age-related pancreatic exocrine insufficiency.[124] However, risks of bleeding and cardiopulmonary complications have been shown as predominant adverse effects among the elderly.[125] Risk of bleeding is attributable to higher rates of anticoagulant use, performance of precut sphincterotomy, therapeutic maneuvers, and PADs. Cardiopulmonary events can be hypothesized to result from higher ASA grading, comorbidity burden, and sensitivity to sedation.

Treatment of complications

Cholangitis

- Conservative management: conservative management for acute cholangitis includes volume expansion, correction of electrolyte abnormalities, and, especially among elderly patients, monitoring for organ dysfunction. Advanced age greater

Table 1
Post–endoscopic retrograde cholangiopancreatography complications, their predispositions, age-related cumulative incidence, and preventive strategies

Adverse Events	Predisposing Factor	Outcomes in Elderly[a]	Preventive Strategies
Post-ERCP pancreatitis	Patient-related factors: younger age, female, history of PEP, nondilated ducts, normal bilirubin, suspected SOD Procedure-related factors: difficult pancreatic cannulation, sphincterotomy, injections or sampling, precut sphincterotomy	Age $\geq$ 65 y: 13.1 (11.0–15.5) Age $\geq$ 80 y: 18.1 (14.0–23.0) Age $\geq$ 90 y: 12.2 (5.6–23.1)	Prophylactic pancreatic duct stenting Aggressive fluid hydration Chemoprophylaxis rectal indomethacin
Bleeding	Patient-related factors: coagulopathy or thrombocytopenia, anticoagulant therapy within 3 d after the sphincterotomy, active cholangitis, ampullary stone impaction, periampullary diverticula Procedure-related factors: low endoscopist experience, uncontrolled cutting (the so-called zipper cut), needle-knife sphincterotomy, degree of intraprocedural bleeding	Age $\geq$ 65 y: 7.7 (5.7–10.1) Age $\geq$ 80 y: 11.1 (7.7–15.4) Age $\geq$ 90 y: 28.6 (17.8–43.3)	• Blood products transfusion among patients with thrombocytopenia or coagulopathy, delay anticoagulation within 3 d of ERCP performance • Avoid sphincterotomy by balloon sphincteroplasty. Balloon tamponade using standard stone extraction or by balloon tamponade. Prophylactic epinephrine injection, intraprocedural usage of blended current, thermal coaptive coagulation using either a multipolar probe or heater probe device, endoscopic clip placement
Perforation • Free wall • Retroperitoneal • Perforation of the bile or pancreatic duct	Patient-related factors: esophageal stricture, Zenker diverticulum, postsurgical altered anatomy gastric outlet obstruction caused by pancreatic cancer, PAD, SOD, biliary or pancreatic duct strictures Procedure-related factors: mechanical pressure from a rigid duodenoscope, guidewire-related ductal perforation, knife precut access, use of a large extraction balloon in a small-caliber duct	Age $\geq$ 65 y: 3.8 (1.8–7.0) Age $\geq$ 80 y: 4.5 (2.2–8.0) Age $\geq$ 90 y: 1.3 (0–7.5)	—

(*continued on next page*)

Table 1
(*continued*)

Adverse Events	Predisposing Factor	Outcomes in Elderly[a]	Preventive Strategies
Infection	Patient-related factors: jaundice, especially if caused by malignancy; primary sclerosing cholangitis Procedure-related factors: failed or incomplete biliary drainage, endoscopist inexperience, performance of a rendezvous (combined percutaneous/ endoscopic) procedure	Age ≥ 65 y: 16.1 (11.7–21.7) Age ≥ 80 y: 4.1 (2.0–7.5) Age ≥ 90 y: 6.8 (2.2–15.8)	• Before contrast injection, aspiration and lavage of infected bile from an obstructed biliary system • Prompt endoscopic (and, if not possible, percutaneous) decompression • Minimize contrast volume
Cardiopulmonary events	Elderly patients with multiple comorbidities risk aspiration from concomitant gastric outlet obstruction in patients with advanced pancreaticobiliary malignancies	Age ≥ 65 y: 3.7 (1.5–7.6) Age ≥ 80 y: 39.6 (29.7–51.6) Age ≥ 90 y: 8.3 (3.0–17.9)	• Appropriate risk-assessment to minimize cardiopulmonary and sedation-related adverse events • Endotracheal intubation with general anesthesia should be used when indicated

Abbreviations: PEP, post-ERCP pancreatitis; SOD, sphincter of Oddi dysfunction.
[a] Cumulative incidence shown as events more than 1000 ERCPs.

than or equal to 70 years, the presence of medical comorbidities, immunocompromised state, extensive peritoneal involvement, delay in or inadequate source control, and presence of sepsis predispose patients to higher risk of adverse outcomes and warrant broad antimicrobial coverage (**Table 2**).[47] Prior isolation of resistant organisms, health care infections, or recent travel to regions with high prevalence of multidrug-resistant organisms require broader coverage.[126]

- Biliary drainage: timing of interventions is based on severity at diagnosis.[127] Although patients with mild cholangitis need conservative measures, biliary drainage is indicated on failure or inadequate response within 24 hours. Patients with moderate to severe cholangitis need immediate biliary drainage plus conservative measures. Patients with severe cholangitis must be monitored for and require support for organ dysfunction. The choice of drainage procedures includes the following:
  1. Endoscopic drainage has much lower complication rates compared with surgical biliary compression. A study of 207 patients with cholangitis (102 aged ≥80 years vs 105 controls) showed its safety among the elderly, in whom comparable technical success rates, procedural times, and complications rates were observed.[128]
  2. Percutaneous biliary drainage and extraction of CBD calculi is attempted on failure or unavailability of endoscopic interventions.

Table 2
Antibiotic regimen for gallbladder and bile duct infection

Infection	Regimen
Community-acquired acute cholecystitis of mild to moderate severity	Cefazolin, cefuroxime, or ceftriaxone
Community-acquired acute cholecystitis with severe physiologic disturbance, advanced age, or immunocompromised state	meropenem, imipenem-cilastatin, doripenem, or piperacillin-tazobactam alone; or ciprofloxacin, levofloxacin, or ceftazidime or cefepime, each in combination with metronidazole
Acute cholangitis following bilioenteric anastomosis of any severity	Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam, ciprofloxacin, levofloxacin, or cefepime, each in combination with metronidazole
Health care–associated biliary infection of any severity	Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam, ciprofloxacin, levofloxacin, or cefepime, each in combination with metronidazole, vancomycin added to each regimen

3. Surgical CBD exploration and subsequent stone extraction is attempted among individuals with failed endoscopic or percutaneous interventions.

Acute biliary pancreatitis Along with conservative management, stone extraction is indicated via endoscopic intervention (ie, ERCP) among suitable ABP candidates.[129,130] Although earlier convention supported endoscopic removal, recent evidence challenges the performance of routine ERCP, and its benefit is substantiated only among patients with ABP with concomitant cholangitis. Early cholecystectomy in the index admission was supported among patients with mild ABP.[131,132] Delay in cholecystectomy has been associated with complications including colic, pancreatitis, and hospitalizations among these individuals. However, among patients with moderate to severe ABP, cholecystectomy should be delayed.[133,134]

ROLE FOR SPHINCTEROTOMY AMONG NONSURGICAL CANDIDATES

Age and comorbidities may render geriatric individuals with ABP unsuitable for cholecystectomy and subsequently cause recurrent biliary events. Endoscopic sphincterotomy (ES) has been used for prophylaxis among these patients and mitigates the risk of recurrent ABP, biliary events, readmissions, and mortality.[135,136] A recent study showed the protective role of ES for ABP recurrence (adjusted hazard ratio [HR], 0.29; 95% CI, 0.08–0.92; $P = .037$) and any gallstone-related event (HR, 0.46; 95% CI, 0.21–0.98; $P = .043$).[137] Although randomized trials supporting ES among nonsurgical candidates are lacking, a randomized study (Endoscopic Sphincterotomy for Delaying Cholecystectomy in Mild Acute Biliary Pancreatitis [EMILY]) designed to evaluate ES in delaying cholecystectomy is underway.[138]

SUMMARY

With advanced age demographics, gallstone disease and associated complications are projected to have a much higher prevalence. Current advancements in diagnostic and therapeutic modalities have enabled inclusion of geriatric individuals for biliary interventions. However, each procedure needs appraisal for efficacy,

therapeutic targets, safety, and cost-effectiveness. With risk/benefit ratio in mind, formulation of an individualized treatment plan with a multidisciplinary approach is imperative. Accumulating data from cohort studies and randomized trials will address knowledge gaps in various biliary disorders and their response to treatment modalities.

CLINICS CARE POINTS

- Among the geriatric population with acute cholecystitis, symptoms are atypical and physical signs may be masked by neuropathy. For e.g. Murphy sign has a lower sensitivity of 48% among the elderly. Typical leukocytosis and bandemia may be also obscured. Diagnostic sensitivity and specificity of acute cholecystitis was found to be 88% and 80% respectively.[24]Patients with acute cholecystitis warrant risk stratification followed by definitive drainage. Cholecystectomy is preferred treatment and high risk patients need temporizing measures.[48-50] Elderly individuals with higher ASA grades and comorbidity burden, have high peri-operative morbidity and biliary and vascular injury.[62,63]Acute cholecystitis with complications, sepsis and hemodynamic instability warrant emergent cholecystectomy.
- Among the elderly with CBD calculi, 'current evidence supports a significantly lower risk among patients in whom any measures for biliary ductal clearance were taken (12.7%; OR, 0.44 [0.35–0.55]).[97] Risk stratification for choledocholithiasis has been proposed by the Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE).[109,110]
- Uncomplicated choledocholithiasis is managed through CBD stone extraction via endoscopic or, in certain circumstances, surgical routes. Endoscopic and surgical CBD stone extraction have similar safety, although the surgical approach is more invasive.[119] For stones too large to remove en-bloc, lithotripsy via mechanical baskets or cholangioscopic application of laser or electrohydraulic energy enables breaking down stones for removal Acute Cholangitis is diagnosed through evidence of systemic inflammation, cholestasis, and imaging.[101]Among the elderly, acute cholangitis is associated with delayed medical care from masked presentation and significantly higher rates of hypotension, peritonism, renal failure.[104] They are managed through antibiotics, fluids and prompt biliary clearance.
- Among patients with acute biliary pancreatitis, pancreatitis is managed conservatively and undergo risk stratification before biliary clearance. Among mild ABP, ERCP benefits among only patients with concomitant cholangitis. Early cholecystectomy in the index admission was supported among patients with mild ABP and delays have been associated with colic, pancreatitis, and hospitalizations.[131,132]However, among patients with moderate to severe ABP, cholecystectomy should be delayed.[133,134]

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DISCLOSURE

The authors have nothing to disclose.

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