Editorial Commentary

Understanding evidence-based clinical practice guidelines for cholelithiasis 2021

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Cholelithiasis is characterized by impaired metabolism of bile acids, cholesterol and bilirubin resulting in deposition of gallstones within the gallbladder (1). The article by Fujita *et al.* outlines the third revision of the evidence-based practice guidelines issued by the Japanese Society of Gastroenterology (JSGE) on cholelithiasis (2). For these current guidelines, 52 questions were adopted through discussions among committee members, covering epidemiology, pathogenesis, diagnosis, treatments, complications, and prognostic aspects of cholelithiasis in Japan (2). The strengths of recommendations were determined by voting by committee members after assessing current available literature, patient preferences, and cost-benefit balance (2). Similar to the previous guideline (second revision), consensus among committee members was defined as the acquisition of 70% votes or over (2).

Epidemiology

Although no data is available on the prevalence of cholelithiasis, it is assumed to have increased in Japan due to rising rates of obesity and biliary surgery (2).

Causes

Based on the mechanism of gallstone formation, they can be divided into three types (2,3):

(I) *Cholesterol stones*: resulting from supersaturation of cholesterol in bile and decreased gallbladder contractility.
(II) *Calcium bilirubinate stones*: resulting from biliary infection and cholestasis.
(III) *Black stones*: resulting from increased unconjugated bilirubin levels (i.e., hereditary spherocytosis, thalassemia, Crohn's disease, ileal resection, liver cirrhosis, etc.).

Risk factors

Risk factors implicated in the development of cholelithiasis

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include forty years of age, fertile females, obesity, high fat diet, dyslipidemia, previous upper gastrointestinal surgery, and bariatric surgery (2,4).

Based on current literature, there is no clear evidence that gallstones are a risk factor for cholangiocarcinoma as studies demonstrate contradictory findings (2). However, porcelain gallbladder and atrophic gallbladder are considered high-risk factors for cholangiocarcinoma (2). Hepatolithiasis has also been identified to be a strong risk factor for intrahepatic cholangiocarcinoma (2).

Clinical features

About 70% of patients with cholelithiasis are asymptomatic with a 10-year symptomatic rate of approximately 10–20%; however, characteristic symptoms include abdominal pain after oral intake with associated nausea and vomiting (2). The presence of fever represents progression to acute cholecystitis (5). Patients with common bile duct stones (CBDS) usually present with abdominal and/or back pain, nausea/vomiting, fever, and jaundice (2,5). Furthermore, patients with hepatolithiasis are often observed to have abdominal pain, fever and jaundice (2).

Diagnosis

Abdominal ultrasound (US) and elevations in alkaline phosphatase (ALP) can help establish a diagnosis of cholelithiasis. In cases of poor gallbladder visualization, indeterminate US findings, suspected CBDS/acute cholangitis, confluence stones, Mirizzi syndrome, or concomitant gallbladder cancer, additional abdominal imaging with computed tomography (CT), magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP), or endoscopic ultrasonography (EUS) followed by endoscopic retrograde cholangiopancreatography (ERCP) is recommended (2). Furthermore, a diagnosis of acute cholecystitis can be established based on clinical features, systemic inflammatory findings, and abdominal imaging (2).

In patients with suspected hepatolithiasis, in addition to blood tests, US, and MRI/MRCP, measurement of tumor markers (CEA and CA19-9) is recommended (2). If intrahepatic stones are visualized, a detailed examination should be performed to identify intrahepatic cholangiocarcinoma; however, in cases where they cannot be visualized or patients have characteristic symptoms, direct cholangiography, bile duct cytology, and cholangioscopy are recommended (2).

Treatment

Treatment approaches for cholelithiasis can be divided into three broad categories as outlined below (2).

(I) Non-surgical management:
- Acute attacks: utilization of medications such as butylscopolamine, flopropione, and nonsteroidal anti-inflammatory drugs during acute episodes.
- Prophylaxis: oral ursodeoxycholic acid (UDCA).
- Minimally invasive techniques: extracorporeal shock wave lithotripsy (ESWL) and oral chemical dissolution therapy. Both techniques are rarely used in clinical practice in recent years.

(II) Endoscopic management:
- ERCP with or without stent placement.

(III) Surgical management:
- Laparoscopic cholecystectomy: preferred surgical management.
- Open cholecystectomy.

Overall, the treatment of cholelithiasis is based on symptomatology and presence or absence of acute cholecystitis. For asymptomatic patients, observation is recommended while carefully assessing for the presence of concomitant gallbladder cancer (2). Elective laparoscopic cholecystectomy should be considered in patients with symptomatic cholecystolithiasis without acute cholecystitis who at high risk of gallbladder cancer such as those with stones >3 cm, polyps >10 mm, porcelain gallbladder, atrophic gallbladder, thickened gallbladder walls, and stone-filled gallbladders (2).

In patients with symptomatic cholecystolithiasis and concomitant acute cholecystitis, initial treatment consists of nothing per oral (NPO) status, aggressive intravenous fluid administration, and initiation of antibiotics with gram negative and anaerobic coverage is recommended for all patients (2). The decision to perform elective laparoscopic cholecystectomy is complex and based on the severity of acute cholecystitis (2):

(I) *Mild acute cholecystitis*: early/elective laparoscopic cholecystectomy is recommended.

(II) *Moderate acute cholecystitis*: early laparoscopic cholecystectomy is recommended. However, if the patient cannot withstand early surgical intervention, gallbladder drainage is recommended followed by elective laparoscopic cholecystectomy.

(III) *Severe acute cholecystitis*: early laparoscopic cholecystectomy by a skilled surgeon at a tertiary medical institution is recommended if the patient has good American Society of Anesthesiologists (ASA) Physical Status (PS) score, no lethal organ damage (respiratory/central nervous system disturbance, or jaundice with total bilirubin >2 mg), treatment responsive damage (circulatory or renal failure/impairment recovering with therapy), and good response to initial therapy. However, if the patient cannot withstand emergent/early surgical intervention, gallbladder drainage is recommended. After gallbladder drainage, PS guides surgical intervention. Elective laparoscopic cholecystectomy is recommended for patients with good PS, while gall bladder preservation is recommended for patients with poor PS score.

Gallbladder drainage plays a key role in management of symptomatic cholecystolithiasis with moderate or severe acute cholecystitis. Although there are several methods of gallbladder drainage [percutaneous transhepatic gallbladder drainage (PTGBD), percutaneous transhepatic gallbladder aspiration, and endoscopic (transpapillary or EUS-guided) gallbladder drainage], PTGBD is the preferred method for high-surgical risk patients due to a success rate (technical success: 97–100% and clinical success 89.3–97.6%) and lower rates of complications (3–39.5%) (2). However, an alternative method, endoscopic transpapillary gallbladder drainage (ETGBD), may be the treatment of choice over PTGBD in patients for patients with suspected CBDS, coagulation abnormalities, antithrombotic medications, presence of ascites, and conditions where PTGBD is difficult to perform or in patients with high risk of PTGBD-related complications (2).

The standard treatment for Mirizzi syndrome, characterized by CBD stricture due to extrinsic compression of the common hepatic duct due to gallstone/inflammation at the neck of the gallbladder, is open cholecystectomy and fistula closure (2). Laparoscopic cholecystectomy may be attempted by skilled surgeons, but it carries a higher risk of complications, and may ultimately require conversion to open cholecystectomy (8–76%) (2). Endoscopic treatment [peroral cholangioscopy (POCS) with electrohydraulic lithotripsy or YAG laser] is indicated in Mirizzi syndrome type 2; however, due to its limited availability, the strength of recommendation for its utilization is weak (2).

Management of CBDS is complex and depends on the presence or absence of cholecystolithiasis and/or complications such as gallstone pancreatitis and acute cholangitis (2):

(I) *Asymptomatic CBDS*: stone removal (usually endoscopic) is performed due to the risk of developing severe cholangitis and other complications.

(II) *CBDS with gallbladder stones*: treatment options include endoscopic bile duct stone extraction followed by surgical (open/laparoscopic) cholecystectomy (two-staged combined treatment) or surgical CBDS removal plus surgical cholecystectomy (one-staged surgical treatment). Both procedures are equally effective, but the two-staged combined treatment, most commonly performed in Japan, has a longer length of hospital stay.

(III) *CBDS with acute cholangitis*: single session endoscopic stone removal is recommended and can be performed safely. Bile duct drainage (endoscopic biliary drainage with stent placement or endoscopic nasobiliary drainage) only in the first session followed by scheduled stone removal is suggested depending on the patient's overall condition and if there is difficulty in performing single session endoscopic stone removal.

(IV) *CBDS with biliary pancreatitis*: early routine ERCP is not recommended for all patients with biliary pancreatitis. Early endoscopy is suggested for biliary pancreatitis with definite/suspected acute cholangitis. However, if endoscopic therapy is difficult (postoperative bowel reconstruction or unsuccessful transpapillary cannulation), percutaneous transhepatic biliary drainage should be considered to manage cholangitis. Furthermore, for large/multiple bile duct stones, endoscopic papillary large balloon dilation is recommended. In cases of giant CBDS, ESWL or POCS can be performed; however, there is little evidence to recommend use.

In elderly patients and those with serious underlying comorbidities with CBDS, endoscopic stone removal is recommended over permanent biliary stenting (2). Permanent biliary stenting should be considered only in patients with a poor prognosis (2). For all CBDS patients with gallstones, cholecystectomy is recommended after endoscopic choledocholithotomy (2). However, for those without gallstones, there is lack of evidence to recommend additional cholecystectomy after endoscopic choledocholithotomy (2). The efficacy of UDCA in preventing recurrence after CBDS removal has not been

proven (2).

The management of hepatolithiasis depends on the presence/absence of intrahepatic cholangiocarcinoma. For asymptomatic hepatolithiasis without concomitant cholangiocarcinoma, liver atrophy, biliary stricture/dilation, follow-up (imaging studies and tumor markers) without surgery is suggested (2). Hepatectomy is indicated in patients with cholangiocarcinoma and/or liver atrophy (2). It can also be considered in patients with failed nonsurgical treatments [i.e., ESWL, percutaneous transhepatic cholangioscopic lithotripsy, EUS-guided hepaticogastrostomy, endoscopic retrograde cholangiography (ERC), balloon-assisted ERC, with stone extraction, and POCS] (2).

In conclusion, the third revision of the evidence-based practice guidelines issued by the JSGE on cholelithiasis aims to support clinicians in the complex decision-making process for management of cholelithiasis to ensure excellent clinical outcomes, and decreased patient morbidity, mortality, and complication rates in Japan.

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Footnote

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