MANAGEMENT OF UNCOMPLICATED GALLSTONES AND BENIGN GALLBLADDER DISEASE

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Calculous Biliary Disease

Gallstones have an estimated prevalence of 5.3 to 8.9% in men and 13.9 to 26.7% in women, making gallstone disease one of the most common problems encountered by general surgeons. Gallstone disease is associated with a number of modifiable and nonmodifiable risk factors. These risk factors include family history (notably first-degree relatives), ethnicity, older age, female gender, diet, obesity, metabolic syndrome, female sex hormone use or excess, pregnancy, low physical activity, terminal ileum resection, Crohn disease, cystic fibrosis, chronic liver disease, gastric surgery, rapid weight loss, certain medications (including octreotide, statins, and ceftriaxone), hematologic disorders resulting in increased hemolysis (including sickle cell disease, thalassemia, hereditary spherocytosis), and prolonged total parenteral nutrition.1,5

ASYMPTOMATIC GALLSTONES

Only 20% of patients with gallstones will develop symptoms. The incidence of complications related to calculous biliary disease is estimated to be 1 to 4% per year in patients with clinically silent gallstones. At the present time, there is no definitive evidence to guide the management of asymptomatic gallstones,4 but given the low rate of complications and symptom development, asymptomatic stones are usually managed expectantly. However, some distinct patient populations merit special consideration regarding the treatment of clinically silent gallstones [see Table 1]. Clear indications for cholecystectomy in the presence of asymptomatic stones include an increased suspicion of malignancy due to the concomitant presence of gallbladder polyps greater than 1 cm in diameter and ethnicity associated with a high risk of developing gallbladder cancer (American Indians, Mexican Americans, Maori population of New Zealand, individuals from Bolivia, Columbia, and Chile). Patients from high-risk ethnic groups have a more than fourfold increased risk of gallbladder carcinoma when gallstones are present and warrant elective cholecystectomy even if stones are asymptomatic. For many years, the presence of a porcelain gallbladder was considered an absolute indication for cholecystectomy based on data from the 1950s documenting gallbladder cancer incidence rates as high as 60% in this population.5,6 Recent studies estimate the prevalence to be between 0.7 and 7%, making cholecystectomy more controversial.5,6

The relative risk of cancer for patients with large asymptomatic gallstones (> 3 cm) is unclear, leading to controversy regarding elective cholecystectomy in this group. The available data are based on older epidemiologic studies that found the relative risk of gallbladder cancer in patients with stones 3 cm or greater was 9.2 (95% confidence interval 2.3 to 37) compared with patients with small stones (< 1 cm).7 Special consideration should also be given to posttransplantation patients, those with chronic hemolytic syndromes, and patients living in very remote areas with limited access to care.8

SYMPTOMATIC GALLSTONE DISEASE

Symptomatic, uncomplicated gallstone disease (biliary colic) is one of the most common manifestations of gallstones and is due to contraction of the gallbladder against a transiently obstructed cystic duct.9 Classic symptoms of biliary colic include right upper quadrant or epigastric pain that occurs after eating (especially fatty meals) and lasts from 30 minutes to several hours. Abdominal pain may be accompanied by diaphoresis, nausea, and vomiting. The most common complications related to gallstones include acute cholecystitis, choledocholithiasis, and gallstone pancreatitis. Uncommon complications include empyema, cholecystoenteric fistula, and gallstone ileus. Complicated gallstone disease is discussed in another chapter.

Table 1 Indications for Elective Cholecystectomy in Asymptomatic Gallstones8

<table>
<thead>
<tr>
<th>Clear indications</th>
<th>Relative indications</th>
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<tbody>
<tr>
<td>Gallstones associated with gallbladder polyps &gt; 1 cm</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Calcified (porcelain) gallbladder</td>
<td>Vague dyspeptic symptoms in the presence of gallstones</td>
</tr>
<tr>
<td>High-risk ethnic groups</td>
<td>Nonfunctioning gallbladder</td>
</tr>
<tr>
<td>Large (&gt; 3 cm) gallstones</td>
<td>Small stones (&lt; 3 mm) with patent cystic duct</td>
</tr>
<tr>
<td>Transplant patients</td>
<td>Unclear indications</td>
</tr>
<tr>
<td>Chronic hemolytic syndromes</td>
<td>Patients living in remote areas</td>
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<tr>
<td>Concomitant cholecystectomy during another abdominal surgery</td>
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</tr>
</tbody>
</table>

* The authors and editors gratefully acknowledge the contributions of the previous authors, Liane S. Feldman, MD, FRCS(C), FACS, and Dennis R. Klassen, MD, FRCS(C), FACS, to the development and writing of this chapter.

Financial disclosure information is located at the end of this chapter before the references.
IMAGING

Ultrasoundography

Classically, ultrasonography has been the diagnostic test of choice for the diagnosis of gallstones. Ultrasonography provides diagnostic accuracy (sensitivity and specificity > 95%) while being noninvasive, readily available, low cost, and radiation free. Ultrasonography can detect the number and size of stones, the presence of sludge or polyps, and the thickness of the gallbladder wall. Ultrasonography can also determine if the ductal system is dilated (associated with obstruction of the biliary tree). Although ultrasonography has many advantages, factors such as operator dependence and challenges imposed by patient body habitus represent potential limitations. It is important for the clinician to be familiar with the skill of the radiologist interpreting ultrasound examinations that form the basis for clinical decision making.

Magnetic Resonance Cholangiopancreatography

Magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS) are highly accurate for the diagnosis of gallstones, with sensitivities of 100% and 98%, respectively. Although these modalities are not commonly required for the diagnosis of gallstones, they may be helpful in certain situations. For example, in the presence of high suspicion but negative ultrasound findings, magnetic resonance imaging (MRI) and EUS may help detect very small stones missed by ultrasonography. In the setting of suspected cholecdocholithiasis, these modalities appear to be superior to ultrasonography because they provide more detailed information about the extrahepatic biliary tree.

Computed Tomography

The use of computed tomography (CT) in biliary colic is limited by the fact that 60 to 80% of gallstones are not radiopaque, although CT may help rule out other causes of abdominal pain. CT is not the diagnostic procedure of choice in patients with asymptomatic gallstones.

TREATMENT OF UNCOMPLICATED SYMPTOMATIC GALLSTONES

Whereas asymptomatic gallstones can be observed as the risk of developing complications is very low, symptomatic gallstones warrant cholecystectomy. Following a first episode of biliary colic, approximately 70% of patients will experience further episodes. Patients with biliary colic have an increased risk of developing gallstone-related complications; within 1 year, an estimated 14% will develop acute cholecystitis, 5% will develop gallstone pancreatitis, and 5% will develop choledocholithiasis. As such, elective cholecystectomy should be considered the standard of care following the diagnosis of biliary colic. In 2013, this is most often performed laparoscopically.

Operative Management

Laparoscopic cholecystectomy

Preoperative evaluation

To plan the surgical procedure, assess the likelihood of conversion to open cholecystectomy, and determine which patients are at high risk for common bile duct (CBD) stones, the surgeon must obtain certain data preoperatively, including the patient history, imaging studies, and laboratory tests.

History and physical examination. A good medical history provides information about associated medical problems that determine the patient’s surgical risk and may affect the patient’s tolerance of pneumoperitoneum. Patients with cardiac or respiratory disease may have difficulty with the effects of CO₂ pneumoperitoneum on cardiac output, lung inflation, acid-base balance, and the ability of the lungs to eliminate CO₂. Most bleeding disorders can be identified through the history. A disease-specific history is important to identify patients in whom previous episodes of acute cholecystitis may make laparoscopic cholecystectomy more challenging, as well as those at increased risk for choledocholithiasis (including patients with a history of jaundice, pancreatitis, or cholangitis). Physical examination will provide the surgeon with information important to plan the surgical access; abdominal wall scars, stomas, or hernias should be taken into account when planning the operative approach.

Imaging studies. Review of previously performed imaging studies helps the surgeon anticipate potential challenges or special considerations. Large stones visualized with ultrasonography may indicate that a larger incision in the skin and fascia will be necessary to retrieve the gallbladder. Small stones increase the likelihood of stone migration into the CBD and may influence the use of intraoperative cholangiography. A shrunken gallbladder and thickened gallbladder wall are significant predictors of conversion to open cholecystectomy. The presence of a dilated CBD or CBD stones visualized preoperatively is predictive of choledocholithiasis. Preoperative or intraoperative imaging of the CBD is indicated when choledocholithiasis is diagnosed or highly suspected. If the patient has undergone endoscopic retrograde cholangiopancreatography (ERCP) or MRCP preoperatively, the images should be reviewed by the surgeon in advance of surgery. The biliary tract has many anatomic variants. Identification of the anatomy in advance of surgery can be useful for the surgeon to avoid surgical complications; however, it is not routinely performed in the absence of other indications.

Laboratory tests. Preoperative blood tests should include a liver function test and complete blood count in most patients and renal function, electrolyte, and coagulation studies in appropriately selected patients. Abnormal bilirubin or liver enzymes may signal an increased risk of choledocholithiasis or primary hepatic dysfunction.

Selection of patients

Patients eligible for outpatient cholecystectomy. Patients in good general health (American Society of Anesthesiologists score ≤ 3), especially if they are at low risk for conversion to laparotomy, are candidates for outpatient cholecystectomy. These patients can generally be discharged 4 to 8 hours after surgery provided that there were no operative complications, their vital signs are stable, they can manage at least a liquid diet without vomiting, and their pain is controllable with oral analgesics. Although institutional practices vary, an estimated 60 to 94% of patients can be successfully discharged on the day of surgery. Patient selection and appropriate patient education are keys to a successful ambulatory surgery program.
Technically challenging patients. Before performing laparoscopic cholecystectomy, the surgeon can often predict which patients are likely to be technically challenging. Patients with difficult body habitus, including those with severe kyphoscoliosis, those with morbid obesity, or those with noncompliant abdominal walls (muscular, burns, previous abdominoplasty, incisional hernia repairs with mesh), present certain technical challenges. Patients with a history of abdominal operations, especially those in the upper abdomen, and those who have a history of peritonitis are likely to pose difficulties because of peritoneal adhesions.17 Patients with previous incisional hernia repair with large mesh may have a very noncompliant abdominal wall, and those with intraperitoneal mesh may have very dense adhesions. These adhesions make access to the abdomen more risky and exposure of the gallbladder more difficult. Patients who have undergone gastroduodenal surgery, have a history of acute cholecystitis, have a long history of recurrent biliary colic attacks, and have recently had severe pancreatitis are particularly difficult candidates for laparoscopic cholecystectomy. These patients may have dense adhesions in the region of the gallbladder, the anatomy may be distorted, the cystic duct may be foreshortened, and the CBD may be very closely and densely adherent to the gallbladder. Such patients are a challenge to even experienced laparoscopic surgeons. When significant problems are encountered, conversion to open cholecystectomy should be considered early in the operation.

Contraindications and special considerations. Poor surgical candidates. There are few absolute contraindications to laparoscopic cholecystectomy. Certainly, no patient who poses an unacceptable risk for open cholecystectomy should be considered for laparoscopic cholecystectomy as conversion to open surgery is always possible. Furthermore, very frail patients and those with considerable medical comorbidities, recent cardiac stent insertion, and limited life expectancy should be considered for nonsurgical management of gallstone disease.

Hernias and stomas. Ventral, inguinal, or femoral hernias are not an absolute contraindication to laparoscopic cholecystectomy. Large hernias may present a problem, however, because gas preferentially fills the hernia on insufflation. Patients with large inguinal hernias may require an external support to minimize this problem and the discomfort related to pneumoscrotum. In patients with small umbilical hernias, it may be appropriate to repair these hernias while they are undergoing laparoscopic cholecystectomy. For such patients, the initial trocar can be placed through the defect by open insertion using the Hasson technique, with care taken to avoid injury to the contents of the hernia. The sutures required to close the hernia defect can be placed before the insertion of the initial trocar. For patients with small incisional hernias, laparoscopic cholecystectomy can proceed as usual. The hernia may be repaired at the same operation if the cholecystectomy goes smoothly and there is no peritoneal contamination. For large incisional hernias, we would proceed with laparoscopic cholecystectomy, limiting adhesiolysis to only that which is required to safely perform the procedure. Patients with stomas may also undergo laparoscopic cholecystectomy provided that the appropriate steps are taken to prevent injury to the bowel during placement of trocars and division of adhesions.

Cirrhosis and liver disease. Patients with cirrhosis or portal hypertension are at high risk for morbidity and mortality during cholecystectomy. If absolutely necessary, laparoscopic cholecystectomy may be attempted by an experienced surgeon in well-compensated cirrhotic patients. The risk of bleeding can be minimized by rigorous preoperative preparation with clotting factors and platelets when necessary. Care should be taken when inserting trocars to avoid large collateral vessels in the abdominal wall as much as possible. Noncutting trocars may be helpful to decrease the risk of hemorrhage from the abdominal wall. Intraoperatively, meticulous dissection and attention to staying in the correct plane of dissection minimize bleeding from the liver bed, which can be profuse when encountered. Cautious but liberal use of electrocautery and ultrasonic shears or bipolar tissue welding devices can both help reduce bleeding and control bleeding when necessary. Ascites, when present, is not an absolute contraindication to laparoscopic cholecystectomy. Ascites can be drained and the gallbladder adequately visualized.

Coagulation disorders. Patients with bleeding diatheses, such as hemophilia, von Willebrand disease, and thrombocytopenia, should not be denied laparoscopic cholecystectomy. They require appropriate preoperative and postoperative care and monitoring, and a hematologist should be consulted.

Pregnancy. Following the introduction of laparoscopy, questions were raised about whether laparoscopic cholecystectomy should be performed in pregnant patients; it has been argued that the increased intra-abdominal pressure may pose a risk to the fetus due to decreased uterine perfusion leading to fetal acidosis and distress. However, more recent data suggest that pneumoperitoneum poses minimal risk to the fetus. Current guidelines recommend treatment of symptomatic gallstone disease and acute cholecystitis in all trimesters of pregnancy due to the minimal risk of laparoscopic cholecystectomy and the increased incidence of spontaneous abortion, premature labor, recurrent symptoms, and longer duration of hospitalization with nonoperative treatment.18 In the presence of the enlarged uterus of pregnancy, open insertion of the initial trocar is advised. Positioning of other trocars may have to be modified according to the size and location of the uterus. In the second and especially the third trimester, the uterus can occupy significant space within the abdomen and distort the usual anatomic landmarks and may make port placement, establishment of pneumoperitoneum, and development of adequate working space difficult. Pneumoperitoneum should be kept as low as possible and the patient should be positioned with her right side slightly elevated to prevent impaired venous return due to uterine compression of the inferior vena cava and to position the uterus away from the operative field.

Malignancy. Finally, patients in whom preoperative imaging gives rise to a strong suspicion of gallbladder cancer (such as a poorly circumscribed mass, polyp > 1.8 cm, signs of invasion into the liver or other structures, or periportal lymphadenopathy) should probably undergo open surgical management and consideration should be given to consulting a hepatobiliary surgeon with expertise in biliary oncology.
Nonoperative Management

Nonoperative management of asymptomatic or minimally symptomatic gallstones has been described but is rarely done due to the safety, efficacy, and wide availability of laparoscopic cholecystectomy. Nonoperative treatment may be considered, however, in patients who present extremely poor operative candidates or have other contraindications to cholecystectomy. Options include pharmacologic dissolution with or without extracorporeal shock wave lithotripsy (ESWL). Oral dissolution may be attempted to eradicate gallstones. Typically, oral ursodeoxycholic acid (UDCA) is used. UDCA has few side effects and works best in patients with small stones (< 15 mm), although it is quite costly. Success rates of 26 to 29% have been reported, but recurrent stone formation remains a risk after successful treatment and may require indefinite therapy. ESWL uses shock wave treatment to break gallstones into small fragments that can subsequently be cleared from the gallbladder. ESWL can also convert moderate-sized stones into smaller fragments more readily dissolved with oral bile salt therapy. The success of ESWL depends on the number and size of stones. Candidates for this kind of treatment should have one to three, ideally small, stones. This constitutes roughly 15% of patients with symptomatic gallstones. Success rates are generally low. Ideal candidates, such as patients with a single stone with a diameter less than 2 mm, have reported success rates as high as 75%. However, patients with single larger stones or two to three stones have success rates in the range of 3 to 45%. Up to 7% of patients who experience initial success will develop recurrent stones, and complications of the treatment are not uncommon, such as biliary colic (35 to 45%), symptomatic choledocholithiasis (1 to 2%), and pancreatitis (2%).

Biliary Dyskinesia

Biliary dyskinesia is defined as biliary pain in the absence of stones and is made up of two distinct entities: functional gallbladder disorder (FGD) and sphincter of Oddi dysfunction (SOD).

Functional Gallbladder Disorder

FGD is believed to be a consequence of failure of coordinated gallbladder emptying, leading to gallbladder distention and increased pressure, which causes symptoms that closely resemble biliary colic. According to the Rome III criteria, FGD is defined as biliary pain in the absence of gallstones. Specific criteria for diagnosis are listed in Table 2. The diagnosis of this disorder is challenging. Data regarding the optimal treatment of this condition are incomplete; however, cholecystectomy continues to prevail as the treatment of choice.

Diagnosis

A management algorithm for patients with suspected FGD is shown in Figure 1. For patients presenting with right upper quadrant pain consistent with biliary colic, standard investigations should include abdominal ultrasonography, liver function tests, and amylase and/or lipase. In the absence of sludge or gallstones on a transabdominal sonogram, EUS should be considered, especially for patients with a difficult body habitus or a technically suboptimal ultrasound examination. Upper endoscopy is useful to rule out peptic ulcer disease or upper gastrointestinal lesions that could be a source of the patient’s symptoms.

The cholecystokinin (CCK) stimulation test, which aims to prove symptom correlation with gallbladder stimulation, was previously used as a method to identify patients with FGD and to improve patient selection for treatment. However, reproducibility of pain is a subjective outcome, and this test has since been shown to be unreliable in the identification of patients who benefit from treatment of FGD (usually cholecystectomy). Cholecystectomy has been shown to improve symptoms whether or not a preoperative CCK stimulation test is positive; and the use of this test for surgical planning in FGD has essentially been abandoned.

Abnormal gallbladder emptying, as defined by quantitative cholescintigraphy (commonly known as hydroxyimido-diacetate [HIDA] scanning), has become the diagnostic test of choice for FGD. However, debate remains regarding the optimal protocol for conducting this test. Moreover, the definition of impaired gallbladder emptying was derived only from studying the ejection fraction of a small number of healthy volunteers. Yap and colleagues found that the maximum mean ejection fraction in 40 patients occurred 15 minutes after CCK infusion and was 74.5%. Three standard deviations below the mean were then arbitrarily set as the lower limit of “normal.” Based on these data, they propose that an ejection fraction less than 40% at 15 minutes be considered abnormal.

The utility of quantitative cholescintigraphy to select patients for cholecystectomy remains poorly characterized. A systematic review recently found no high-quality trials in this area and concluded that further study is necessary. The best available data come from a small randomized controlled trial...

### Table 2: Rome III Criteria for the Diagnosis of Functional Gallbladder Disorder

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Supportive criteria</th>
<th>Mandatory for the diagnosis of functional gallbladder disorder</th>
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</thead>
<tbody>
<tr>
<td>Episodes of pain in the right upper quadrant or epigastrium and all of the following:</td>
<td>Pain with one or more of the following:</td>
<td>Gallbladder present</td>
</tr>
<tr>
<td>Pain lasts 30 minutes or more</td>
<td>Nausea/vomiting, radiation to back and right subscapular area, awakening from sleep due to pain</td>
<td>Normal liver enzymes, conjugated bilirubin, amylase, and lipase</td>
</tr>
<tr>
<td>Pain occurs at different intervals (not daily)</td>
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<tr>
<td>Pain builds up to a steady level</td>
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<td></td>
</tr>
<tr>
<td>Pain is severe enough to interrupt patient’s daily activities and/or lead to emergency department visits</td>
<td></td>
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</tr>
<tr>
<td>Pain is not relieved by bowel movements, postural changes, or antacids</td>
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<tr>
<td>Other structural diseases that could explain the pain have been ruled out</td>
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controlled trial in which patients with abnormal cholescintigraphy experienced 91% symptom resolution after cholecystectomy.\(^26\) Another series confirmed these findings\(^32\); however, other studies have found no difference in symptom resolution with cholecystectomy or observation,\(^33\) and the use of quantitative cholescintigraphy in selecting patients for cholecystectomy remains controversial.

**Natural History**

The natural history of patients with FGD remains poorly characterized, although the evidence suggests that patients with genuine FDG tend to remain symptomatic without treatment.\(^34\)

Evidence for the progressive nature of FGD comes from a study examining bile crystals and gallbladder wall pathology in 72 cholecystectomy specimens, half of which did not have gallstones. This study found no difference in gallbladder ejection fraction or histologic evidence of chronic cholecystitis between groups, and the authors concluded that gallbladder stasis exists on a spectrum and that, eventually, patients with acalculous biliary colic would develop gallstones if left untreated.\(^35\) However, this theory has not been proven, and as long as long-term follow-up data and adequately powered prospective studies are lacking, the true natural history of functional gallbladder disorder will remain unclear.

**Treatment**

Evidence regarding the best treatment for FDG is lacking. A recent Cochrane review\(^36\) found only one randomized controlled trial that examined cholecystectomy versus observation for FDG, and the study was evaluated to be at high risk for bias. This trial did report 91% symptom resolution with cholecystectomy and 100% symptom persistence without it, although the trial enrolled only 21 patients.

A meta-analysis of cholecystectomy versus observation reported five trials that met inclusion criteria for analysis.\(^34\) Four of these studies were retrospective chart reviews, and one prospectively randomized patients to cholecystectomy or observation. Inclusion criteria for the meta-analysis required studies that divided biliary dyskinesia patients into cholecystectomy or observation groups and reported on symptoms at follow-up. In the pooled data of 274 patients, surgical therapy for acalculous biliary pain resulted in 98%...
symptom improvement over a mean follow-up of 22 months. The authors concluded that in the era of laparoscopic cholecystectomy, the value of surgical therapy for FGD outweighs the risks and should be the treatment of choice in lieu of observation alone.

Summary

FGD has been described for many decades; however, the optimal investigation and treatment of this disease remain incompletely understood. Patients who meet the Rome III criteria for FGD and are fit for surgery should be offered cholecystectomy after appropriate discussion and informed consent. Well-designed, appropriately powered, randomized controlled trials evaluating the utility of CCK cholecintigraphy in selecting patients for operative intervention, as well as trials to assess the risks and benefits of surgical treatment versus observation alone, are needed to better characterize the optimal management of this disorder.

Sphincter of Oddi Dysfunction

SOD represents either mechanical or functional obstruction at the muscular valve that regulates the flow of bile from the bile duct into the duodenum. Multiple terms have been used to refer to this entity, including papillary stenosis, sclerosing papillitis, postcholecystectomy syndrome, and tachyoddia; confusion in the literature stems from this unclear nomenclature. Regardless of the name, however, this syndrome is associated with two distinct clinical entities: recurrent biliary pain and recurrent idiopathic pancreatitis. Given that these pain syndromes can overlap with other causes of abdominal pain, caution must be used in clearly delineating the cause of pain as being consistent with SOD. To avoid unnecessary diagnostic tests, the Rome III criteria were developed to aid clinicians in identifying patients at high risk for SOD who would benefit from further testing and/or treatment [see Table 3]. Patients must experience discrete episodes of self-limited epigastric and right upper quadrant pain without any other structural abnormality that could be the cause.

Biliary SOD is diagnosed only in postcholecystectomy patients as the presence of a gallbladder with recurrent biliary pain and no gallstones leads to a diagnosis of biliary dyskinesia. In a large survey of patients after cholecystectomy, the reported incidence of persistent or recurrent abdominal pain was 14 to 20%, with 1.0 to 1.5% reporting pain consistent with SOD. For biliary SOD, pancreatic enzymes must be normal, whereas for pancreatic SOD, amylase and lipase should be elevated. The gallbladder may be present for the diagnosis of pancreatic SOD, but mechanical causes for the patient’s symptoms (such as gallstones or gallbladder sludge) must be carefully ruled out.

For biliary SOD, the Milwaukee Classification was initially described in 1988 by Hogan and Geenen to differentiate patients with varying degrees of likelihood of benefiting from ERCP and sphincterotomy [see Table 4]. Patients with elevated liver enzymes and associated pain on two occasions, a dilated CBD, and delayed drainage of the bile duct on ERCP are likely to have abnormal sphincter of Oddi manometry. The Rome committee subsequently refined these criteria in its third revision to favor transabdominal ultrasonography in the diagnostic workup over ERCP, with the intention of minimizing the number of patients offered ERCP, with its inherent risks and complications. Rates of abnormal sphincter of Oddi manometry (SOM) decrease when fewer Rome or Milwaukee criteria are present.

Pancreatic SOD has similarly been classified according to types, although this classification system is less commonly used [see Table 5]. Similar to the biliary SOD classification systems, patients are divided into three groups based on the number of criteria they fulfill, and rates of elevated pancreatic SOM vary predictably by type, with type I having the highest correlation.

Laboratory Investigations

Investigations for possible SOD should be directed toward the criteria identified by the Rome III committee as having high diagnostic yield [see Table 3]. These include liver profile and pancreatic enzymes, ideally measured during an episode of pain.

Diagnostic Imaging

Sphincter of Oddi Manometry

SOM is an invasive diagnostic test that is widely considered the gold standard for diagnosis of biliary or pancreatic SOD. For the purposes of diagnosing SOD, pressures greater than 40 mm Hg are considered abnormal. This is a highly specialized procedure that should be performed in high-volume centers. Given that the indications for SOM are limited and evaluation of these patients can be conducted electively, at this time, it is appropriate to limit these tests to such centers that can demonstrate the requisite reproducibility and low complication rate. The morbidity rate of SOM can be quite high, particularly in small ducts and because SOD is a known independent risk factor for pancreatitis after ERCP.

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Several noninvasive tests have been described to diagnose SOD. All have the benefit of avoiding ERCP and SOM, with their inherent risks; however, their diagnostic accuracy in SOD varies.

Transabdominal Imaging
Abdominal ultrasonography is usually the first imaging modality employed and has high diagnostic yield for ruling out gallstones or other mechanical causes of biliary obstruction. When ultrasonography cannot completely visualize the biliary and pancreatic ducts, additional modalities, such as MRCP, abdominal CT, and EUS, can be helpful to rule out strictures, microlithiasis, tumors, or other structural causes of symptoms.

Sphincter Stimulation Tests
A recent systematic review of noninvasive tests for SOD found the morphine-neostigmine provocation test (which aims to reproduce both symptoms and elevations in serum liver and pancreatic enzymes by stimulating the sphincter of Oddi) lacks specificity, whereas the ultrasonography-secretin stimulation test (which documents dilatations in biliary and pancreatic ducts after a lipid-rich meal or secretin or CCK infusion) lacks sensitivity due to inability to reliably visualize the ducts.

Cholangiography
MRCP has increased in popularity as a noninvasive alternative to ERCP to delineate the anatomy of the biliary system, and this imaging technique has also been applied to the diagnosis of SOD. A prospective evaluation was performed of 47 patients with type II and III biliary SOD who underwent secretin-stimulated MRCP followed by SOM for comparison. Assuming biliary SOM as the gold standard, the diagnostic accuracy of secretin stimulation–MRCP was found to be 73% and 46% in type II and III patients, respectively. Another study of 37 patients with idiopathic pancreatitis and suspected SOD who underwent both secretin stimulation–MRCP and SOM reported sensitivity and specificity of 57% and 100%, respectively; however, secretin stimulation–MRCP could not distinguish whether the biliary or pancreatic sphincter was abnormal.

Hepatobiliary Scintigraphy
In patients with a surgically absent gallbladder, hepatobiliary scintigraphy can image and quantify the passage of bile through the biliary tree and has received the greatest attention as an alternative to SOM. Although less invasive than SOM, the sensitivity and specificity are 49% and 78%, respectively, and the false positive rate is 21% when compared with SOM as the gold standard. Hepatobiliary scintigraphy also performs poorly in identifying patients with type II and III SOD versus type I (44 to 50% versus 90%, respectively).

In summary, several noninvasive tests for SOD exist with variable sensitivity and specificity in comparison with SOM, although SOM testing remains the gold standard. These alternative tests may be of value in patients for whom SOM is unavailable or high risk.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Comparison of Milwaukee Classification of Patients with Biliary Pain without Identifiable Cause prior to Manometry with the Rome III Revision of the Milwaukee Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary SOD</td>
<td>Milwaukee Classification</td>
</tr>
<tr>
<td>Type I</td>
<td>Pain associated with AST and ALT &gt; 2× normal on two occasions</td>
</tr>
<tr>
<td></td>
<td>CBD dilated &gt; 10 mm on sonogram or &gt; 12 mm on ERCP</td>
</tr>
<tr>
<td></td>
<td>Delayed drainage of contrast from the CBD after &gt; 45 min in the supine position</td>
</tr>
<tr>
<td>Type II</td>
<td>One or two of the above abnormalities</td>
</tr>
<tr>
<td>Type III</td>
<td>None of the above abnormalities</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; CBD = common bile duct; ERCP = endoscopic retrograde cholangiopancreatography; SOD = sphincter of Oddi dysfunction; SOM = sphincter of Oddi manometry.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Modified Milwaukee Classifications System for Patients with Pancreatic-Type Pain of Unknown Etiology</th>
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<tbody>
<tr>
<td>Pancreatic SOD</td>
<td>Classification Criteria</td>
</tr>
<tr>
<td>Type I</td>
<td>Pain associated with elevated pancreatic enzymes &gt; 1.5× normal</td>
</tr>
<tr>
<td></td>
<td>Pancreatic duct dilated &gt; 6 mm (head) or &gt; 5 mm (body)</td>
</tr>
<tr>
<td>Type II</td>
<td>One of the above abnormalities</td>
</tr>
<tr>
<td>Type III</td>
<td>None of the above abnormalities</td>
</tr>
</tbody>
</table>

SOD = sphincter of Oddi dysfunction; SOM = sphincter of Oddi manometry.
TREATMENT

Several treatment options exist for SOD; the most common and definitive is sphincterotomy. Figure 2 summarizes a diagnosis and treatment algorithm for patients with suspected SOD.

Sphincterotomy

Sphincterotomy is usually performed endoscopically [see Figure 3], with surgical sphincterotomy/sphincteroplasty being reserved for cases in which the endoscopic approach is not available or not possible due to anatomic constraints. Sphincterotomy does carry a significant risk of complications, however, the most common being acute pancreatitis, bleeding, and duodenal perforation. The rates of these complications in SOD patients vary widely, from 0 to 60%.

Type I biliary SOD patients have high success rates after sphincterotomy, with rates of symptom improvement reported to be between 83 and 100%. Given that type I patients have such high success rates with sphincterotomy, current recommendations are that these patients not undergo SOM due to the complication rates associated with this procedure and the high likelihood of treatment success regardless of manometry results. Type II and III SOD patients present more of a treatment challenge because reported symptom improvements with sphincterotomy are lower than in type I patients. This may represent differences in disease etiology between the two groups as type I is often thought of as stenosis of the sphincter of Oddi complex.

Figure 2  Diagnosis and treatment algorithm for suspected sphincter of Oddi dysfunction (SOD). BT = botulinum toxin; CT = computed tomography; EUS = endoscopic ultrasonography; MRCP = magnetic retrograde cholangiopancreatography; SOM = sphincter of Oddi manometry; U/S = ultrasonography. *Consider noninvasive alternatives to SOM in high-risk patients or if SOM is not available (see text for explanation).
whereas types II and III are thought to represent functional disorders.

Only two randomized trials have examined the success rates of sphincterotomy in type II and III biliary SOD patients, and these were the only studies included in a Cochrane review on this subject. A recent systematic review also addressed this question, including 177 patients overall. Both reviews concluded that the literature supports endoscopic sphincterotomy for type II patients with elevated SOM greater than 40 mm Hg, with an expected symptom improvement rate of 69%. In contrast, only 37% of type III patients improve with sphincterotomy, which was no better than sham sphincterotomy in one randomized study.

Pancreatic SOD is even less well studied than biliary SOD, and no randomized trials have been done examining the value of sphincterotomy in these patients. However, reported success rates in small, noncontrolled series have been reported to be in the range of 54 to 77%.

Medical Therapy

A variety of medical treatments that lower the basal sphincter of Oddi pressure have been proposed, including nifedipine, nitrites, and antispasmodics, although all have been studied in small numbers of patients. Although data supporting medical therapy over sphincterotomy remain somewhat limited, a trial of medical treatment may be warranted in type II patients without elevated SOM and type III patients given the low rate of success of sphincterotomy in these subgroups.

Botulinum Toxin Injection

Botulinum toxin has been injected into the sphincter of Oddi complex to reduce basal pressures with some success, although the improvements last only for several months. The response to botulinum toxin injection in type II and III patients may predict success with endoscopic sphincterotomy.

Summary

SOD can manifest as biliary pain (after cholecystectomy) or pancreatic pain, in which no structural abnormality can be found. Thorough investigation to rule out structural causes is essential before proceeding to further workup and treatment of these disorders [see Figure 2]. Diagnostic tests should be selected to classify patients according to Rome III criteria to inform treatment decisions. Outcomes can be good after endoscopic sphincterotomy in carefully selected patients.

Gallbladder Polyps

Gallbladder polyps are outgrowths of the gallbladder wall. Reported incidences of gallbladder polyps in healthy subjects range from 4.3% (Denmark) to 5.9% (Taiwan), and they are found in 2 to 12% of cholecystectomy specimens. They are often found incidentally by ultrasound examination or on pathologic examination of cholecystectomy specimens. The majority of gallbladder polyps are hyperplastic and benign, although occasionally they harbor malignancy. As the incidence of polypoid lesions of the gallbladder is low, their natural history and thus optimal management remain incompletely understood.

Classification

Polypoid lesions of the gallbladder range on a spectrum from benign mucosal accumulation of lipids, termed cholesterolosis, to malignant lesions, most commonly gallbladder adenocarcinoma. In 1970, Christensen published a review of benign gallbladder polyps found in pathology specimens and proposed a classification system [see Figure 4].

Diagnosis and Imaging

Multiple imaging modalities can detect gallbladder polyps; however, none can reliably distinguish benign lesions from those harboring malignancy, nor can any one diagnostic modality predict the future behavior of gallbladder polyps. However, several imaging modalities can be useful in characterizing and following polypoid lesions of the gallbladder.

Transabdominal Ultrasonography

The majority of gallbladder polyps are found incidentally by transabdominal ultrasonography. If they are initially seen on a sonogram, ultrasonography is also a convenient and low-risk modality with which to serially follow polyps that are not resected. Ultrasonography has poor reliability for detecting small lesions, however, as 36 to 83% of lesions less than 5 mm seen preoperatively by this modality have no mass on pathologic examination after cholecystectomy. Several features on ultrasonography have been shown to correlate more highly with malignant polyps. In a series of 213 patients with a gallbladder lesion identified by preoperative ultrasonography, those greater than 16 mm had a
sensitivity of 85% and a specificity of 93% for malignancy. Other ultrasonographic features that were highly correlated with malignancy were gallbladder wall thickening greater than 5 mm, the presence of gallstones, and invasion at the liver surface. Lesion shape (pedunculated versus sessile), echogenicity, or the presence of flow on a Doppler sonogram did not differ significantly between benign and malignant lesions.

**Endoscopic Ultrasonography**

EUS has been investigated for its utility in differentiating benign and malignant gallbladder polyps due to its enhanced resolution in comparison with transabdominal ultrasonography. Retrospective studies have shown EUS to have greater sensitivity and specificity than transabdominal ultrasonography in differentiating malignant from benign polyps for polyps 1 to 2 cm in size (92% and 88%, respectively, versus 54% for both). Furthermore, high-resolution transabdominal ultrasonography (HRUS) may provide equal accuracy to EUS for polyps greater than 1 cm while being less invasive. Although EUS offers greater diagnostic accuracy for identifying malignant gallbladder polyps than conventional ultrasonography, the major dilemma in the management of gallbladder polyps is for those less than 10 mm [see Treatment, below]. At the present time, EUS alone cannot reliably confirm or rule out malignancy in small polyps; however, it is useful to identify larger polyps at high risk for malignancy, which can aid in appropriate surgical planning.

**Computed Tomography**

Contrast-enhanced CT has similar sensitivity and specificity to HRUS and EUS in distinguishing benign from malignant polyps greater than 1 cm, but the need for intravenous
contrast dye and exposure to radiation limit the usefulness of CT for long-term follow-up of unresected polyps. CT is useful, however, as a staging modality when the risk of invasive malignancy is high.

**Fluorodeoxyglucose Positron Emission Tomography**

The use of fluorodeoxyglucose positron emission tomography (FDG-PET) has been investigated for its ability to distinguish benign and malignant gallbladder polyps. Small series have shown that FDG-PET can identify malignant polyps greater than 1 cm in size in 81% of cases, with a false positive and a false negative rate of 20% and 10%, respectively. At present, FDG-PET is useful for identifying potentially malignant polyps 1 to 2 cm in size but cannot rule out malignancy in smaller polyps.

**TREATMENT**

Longitudinal data regarding the natural history of neoplastic gallbladder polyps are lacking. A recent Cochrane review found no randomized or quasirandomized controlled trials investigating the role of cholecystectomy versus watchful waiting for gallbladder polyps up to 2 cm in size. The main concern regarding polypoid lesions of the gallbladder is the risk of present or future malignancy. What is known about this risk comes almost entirely from observational and retrospective studies examining the incidence of malignant transformation in gallbladder polyps on pathologic examination following cholecystectomy.

The only definitive treatment for gallbladder polyps is cholecystectomy; however, most polyps can be managed without surgery. Indications for surgical intervention depend on polyp size, risk factors for malignancy, and symptoms [see Figure 5].

**Size Criteria**

Size is a key determinant of malignancy risk in gallbladder polyps. Several reviews of pathology specimens have found that of malignant polyps, 88 to 100% of them are greater than 1 cm in size, whereas 85 to 94% of benign polyps are less than 1 cm. As a result of such studies, it is currently accepted that size greater than 1 cm is a risk factor for malignant transformation, and all such patients should be offered cholecystectomy.

Although cholecystectomy alone is sufficient to remove polyps with early malignant transformation (mucosal disease), it is important to identify lesions at risk for harboring more advanced malignancies so that the appropriate diagnostic and surgical treatment may be offered. Whereas polyps less than 1 cm are generally benign and can be observed, polyps greater than 18 mm are frequently invasive. Therefore, it is recommended that polyps greater than 1 cm be resected and, specifically, those greater than 18 mm be treated as gallbladder cancer until proven otherwise.

For polyps less than 1 cm, controversy still exists regarding the optimal management, with some authors recommending cholecystectomy for polyps greater than 6 mm, whereas the majority advocate observation. Longitudinal studies have shown that polyps less than 6 mm rarely increase in size and likely do not need to be followed if stable on serial imaging, whereas cases of malignant transformation in polyps 7 to 9 mm in size have occurred even after 4 years of observation. Although further studies are required to determine the optimal length of follow-up for small polyps less than 1 cm, the present data suggest that polyps less than 6 mm that are stable on follow-up imaging at 6 months to 1 year do not need to be followed further, whereas 7 to 9 mm polyps require extended serial imaging. For cases in which the patient cannot, or does not wish to, comply with long-term follow-up, cholecystectomy may be warranted.

**Concurrent Gallstones and Gallbladder Polyps**

Cholelithiasis is highly correlated with gallbladder cancer, with gallstones conferring a relative risk of 4.9 for

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**Figure 5** Treatment algorithm for polypoid lesions of the gallbladder.
the development of malignancy. However, the incidence of gallbladder cancer remains quite rare, whereas the incidence of gallstones is quite high, so currently, prophylactic cholecystectomy for asymptomatic gallstones is not recommended to prevent the development of malignancy. However, the risk of malignant transformation within gallbladder polyps has been linked to concurrent cholelithiasis. For this reason, cholecystectomy is indicated for known polyps of any size in patients with concurrent cholelithiasis.

**Primary Sclerosing Cholangitis**

Whereas the incidence of malignant gallbladder polyps in the general population varies predictably by size, growth, and the presence of other risk factors for gallbladder cancer, the incidence in patients with primary sclerosing cholangitis (PSC) is much higher due to the increased risk of biliary tract malignancies in these patients. In a retrospective review of 102 patients at the Mayo Clinic with PSC and gallbladder polyps who underwent cholecystectomy, 57% were found to harbor malignancy. A more recent retrospective study of 57 PSC patients who underwent cholecystectomy for a gallbladder mass found that polyp size of 0.8 cm was 100% sensitive and 70% specific for neoplasia. Given that gallbladder polyps in PSC patients confer a much higher risk of malignant transformation than in the general population, even polyps less than 1 cm should be considered for cholecystectomy or close serial observation in high-risk surgical candidates.

**Symptomatic Gallbladder Polyps**

Although the majority of gallbladder polyps are found incidentally, polyps may be found in patients with biliary pain but no gallstones. Cases of detached polyps causing cholecystitis and obstructive jaundice have also been reported. Although rare, in symptomatic patients, cholecystectomy may result in resolution of symptoms. In a study of 45 symptomatic patients with polypoid lesions on imaging but no gallstones, 94% reported resolution of their biliary pain postoperatively. In this series, 43 of 45 patients had polyps less than 5 mm and 40% had evidence of chronic cholecystitis on pathologic examination. Although symptomatic gallbladder polyps are quite uncommon, cholecystectomy is reasonable in an average-risk patient with no other identifiable cause of biliary pain.

**Adenomyomatosis**

Adenomyomatosis of the gallbladder is characterized by thickening of the muscular wall consisting of so-called Rokitansky-Aschoff sinuses and overgrowth of the mucosa. Three distinct types have been described based on their pattern of distribution in the gallbladder wall: fundic (confined to the fundus), segmental (causing stricture of the gallbladder body separating the fundus from the neck), and diffuse. Controversy exists regarding the risk of gallbladder cancer in association with adenomyomatosis as some reports indicate an increased rate of cancer in gallbladders with adenomyomatosis, particularly the segmental type, whereas other studies have not confirmed these results. Patients with the segmental variety who are of acceptable surgical risk may therefore benefit from cholecystectomy, whereas patients with diffuse or fundic adenomyomatosis need not undergo resection.

**References**


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Figure 3 Courtesy of Jeffrey Barkun, MD.