Symptomatic Cholelithiasis and Functional Disorders of the Biliary Tract

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KEYWORDS

• Gallstones • Cholelithiasis • Biliary colic • Gallbladder dyskinesia
• Sphincter of Oddi dysfunction

KEY POINTS

- Symptomatic cholelithiasis is uncomplicated gallstone disease that can be diagnosed through abdominal ultrasound and is treated surgically with cholecystectomy.
- Functional disorders of the biliary tract include functional gallbladder disorder, functional biliary, pancreatic, and combined sphincter of Oddi disorders.
- Functional gallbladder disorder, also known as gallbladder dyskinesia, is associated with decreased gallbladder ejection fraction and is also managed surgically with cholecystectomy.
- The sphincter of Oddi disorders have subclassifications based on anatomy, laboratory analysis, and imaging findings.
- The sphincter of Oddi disorders are typically evaluated with manometry and, in general, managed with endoscopic sphincterotomy when basal sphincter pressures are elevated.

SYMPTOMATIC CHOLELITHIASIS

Gallstone disease is one of the most common and costly conditions in the United States. An estimated 20 million Americans, 6.3 million men and 14.2 million women, have gallbladder disease.[1] The cost of gallstone disease has been estimated at $6.5 billion per year worldwide.[2] The epidemiology and risk factors for gallstones have become well published over the last several decades. Ultrasonography has become the gold standard in diagnosis. Laparoscopic cholecystectomy is the standard treatment.

No Disclosures.
The views expressed herein are those of the authors and do not reflect the official policy or position of the Department of the Army, the Department of Defense, or the US Government.
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Surg Clin N Am 94 (2014) 233–256
http://dx.doi.org/10.1016/j.suc.2013.12.001 **surgical.theclinics.com**
0039-6109/14/$ – see front matter Published by Elsevier Inc.

Epidemiology

The formation of gallstones and gallbladder disease is likely multifactorial and involves an interaction between genetic and environmental factors. Identified risk factors include ethnicity; age; gender; lifestyle; medications; and genetics. The third National Health and Nutrition Examination Survey surveyed a representative sample of greater than 14,000 people in the United States and conducted gallbladder ultrasonography to determine the ethnic distribution of gallstone disease. African American men and women had the lowest prevalence at 5.3% and 13.9%, respectively, whereas Mexican American men and women had a prevalence of 8.9% and 26.7%, respectively, with most other ethnicities falling somewhere in between.[1] Of note, Native Americans have the highest prevalence in North America, with 73% of female Pima Indians over 25 years of age having gallstones.[3] A multicenter, population-based Italian study known as the Multicenter, Population-based Italian study on Epidemiology of Cholelithiasis project identified female gender and increasing age and body mass index as the most significant risk factors for gallstone disease.[4] In addition to obesity, rapid weight loss is also associated with gallstone formation and this patient population is more likely to be symptomatic as well.[5] The higher rates of gallstone disease in women are likely a result of pregnancy and sex steroids.[1,3,6] Moreover, the risk of developing cholesterol gallstones increases with the number of pregnancies. One study reported an increase in the prevalence of gallstones from 1.3% in nulliparous women to 12.2% in multiparous women.[7] A strong familial predisposition also exists for gallstone formation. First-degree relatives of gallstone patients were found to have gallstones over 4 times more often than in a matched control population.[8] Interestingly, mutations in the adenosine triphosphate-binding cassette, subfamily B, member 4 (ABCB4) gene are related to symptomatic cholelithiasis at a younger age (<40 years).[9] Finally, comorbidities such as diabetes mellitus, cirrhosis, hypertriglyceridemia, Crohn, disease, and conditions that lead to bile stasis are associated with gallstone formation.[2]

Pathophysiology

Gallstones are divided into the 3 following types: cholesterol stones, black pigment stones, and brown pigment stones. Cholesterol stones (>50% cholesterol content) are the most common in the Western world and account for approximately 70% of all stones. Black pigment stones account for the remainder of stone carriers in the Western world and can be caused by hemolytic disorders or cirrhosis. Brown pigment stones are seen most commonly in East Asia and are associated with infection of the biliary tree. Currently the prevalence of cholesterol gallstones seems to be increasing worldwide as a result of socioeconomic changes and an increase in a more Western diet.[10] The formation of cholesterol gallstones has been illustrated since the 1960s with variations of Admirand's triangle, which is essentially an equilibrium diagram of bile salt, cholesterol, and lecithin (**Fig. 1**). Supersaturation with cholesterol, a decrease in the quantity of bile salt or lecithin, or a combination of these factors promotes gallstone formation.[11] Many of the previously mentioned risk factors alter the composition of bile, thus leading to the formation of gallstones.

Clinical Presentation

Most patients with gallstones are asymptomatic. The Simione study examined more than 1900 members of a small Italian town and found an incidence of cholelithiasis of 6.9%. Most were asymptomatic with only 22% reporting biliary pain over the previous 5-year period.[12] Only 16% of the asymptomatic patients then went on to develop symptoms over a 10-year follow-up.[13] In another study by Rome Group for the Epidemiology

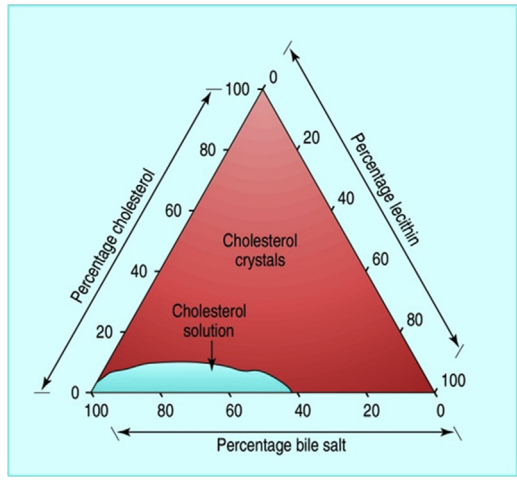

Fig. 1. Adaptation of Admirand's triangular coordinates relating cholesterol, bile salts, and lecithin concentration to cholesterol solubility. (*From* Johnson CD. ABC of the upper gastrointestinal tract. Upper abdominal pain: Gall bladder. BMJ 2001;323:1170; with permission.)

and Prevention of Cholelithiasis, initially asymptomatic patients with gallstones had a cumulative incidence of 26% for the development of biliary pain at 10 years.[14]

Uncomplicated gallstone disease typically presents with upper abdominal pain. A variety of other gastrointestinal complaints have been associated with uncomplicated gallstone disease, such as bloating, belching, nausea, and fatty food intolerance, but these other factors do not consistently discriminate between gallstone disease and other causes.[15] The symptoms are due to gallbladder contraction in the presence of gallstones, which then forces the stone against the outlet, cystic duct, leading to increased pressure in the gallbladder. This increase in pressure, or gallbladder distention, causes the pain, which subsides as the gallbladder relaxes, and the stone falls back from the cystic duct.[16]

Biliary colic is typically steady in quality rather than "colicky" as the name implies. The classic description is a constant, dull discomfort in the right upper quadrant that may radiate to the back. The pain is not relieved or exacerbated by movement, position, or bowel function. Typically, the pain will last greater than 30 minutes with the maximum time being 6 hours.[15] Many patients report postprandial pain; however, association with meals is not universal. In fact, in a significant proportion of patients the pain is nocturnal.[17,18] Recurrent attacks are common and can range from within hours to years.[19] Some patients may present with atypical symptoms such as chest pain, eructation, early satiety, dyspepsia, or nonspecific abdominal pain.

The physical examination and laboratory evaluation are typically benign. Upper abdominal tenderness is frequently noted on physical examination to include voluntary guarding but peritonitis is absent. Laboratory values in uncomplicated gallstone disease should be normal because any abnormalities, such as leukocytosis or elevated liver and pancreatic enzymes, suggest a complication of gallstone disease, including cholecystitis, cholangitis, or pancreatitis.[20]

Diagnostic Procedures

The diagnostic test for gallstone disease is ultrasonography. It is cost-effective, noninvasive, and accurate. Approximately 95% of gallbladder stones will be detected by

ultrasound. Ultrasound can also detect findings associated with complicated gallbladder disease to assist in management. If there are no stones detected on ultrasound and a high suspicion exists, the ultrasound should be repeated.[21]

Ultrasonography findings in gallstones include single- or multiple-echo dense structures in the most dependent portion of the gallbladder. The stones produce a characteristic posterior shadowing due to reflection of the ultrasonic beam.[22] Gallbladder sludge, on the other hand, will not produce an acoustic shadow and is more viscous. It represents microlithiasis, which can also produce biliary colic or lead to complicated gallstone disease such as cholangitis or pancreatitis.[23,24] Endoscopic ultrasound (EUS) can be used to evaluate for occult cholelithiasis in patients with suspected gallstone disease but a negative transabdominal ultrasound. The sensitivity of 96% for occult cholelithiasis and choledocholithiasis exceeds both computed tomographic scan and transabdominal ultrasound.[25]

Treatment and Outcomes

The current standard for management of uncomplicated gallstone disease, or symptomatic cholelithiasis, is laparoscopic cholecystectomy. Medical management consists of oral dissolution therapy with oral bile acids and is reserved for symptomatic gallstone patients who are not a candidate for surgery and have small (equal to or less than 5 mm in size), uncalcified, cholesterol stones in a functioning gallbladder with a patent cystic duct. Oral litholysis uses oral hydrophilic bile acids for dissolution therapy for cholesterol gallstones. Ursodeoxycholic acid is currently used and leads to decreased biliary cholesterol secretion, increased solubility of cholesterol by forming liquid crystals, and reduced intestinal absorption. However this approach is successful only in a small subset of patients; recurrence is common (30%–50% at 5 years), and the cost-benefit ratio is unfavorable.[26] A variety of other medications and pathways have been studied in their effect on gallstone formation, including statins, aspirin, ezetimibe, and nuclear receptors that drive lipid homeostasis in the hepatobiliary and gastrointestinal systems.[27–30] Observational studies report that nutritional modification, such as increased dietary polyunsaturated or monounsaturated fatty acids, fiber, caffeine, vegetable protein, and a diet low in refined carbohydrates, may aid in reduction of symptoms.[31] Overall, most patients will undergo laparoscopic cholecystectomy as definitive and effective management for symptomatic cholelithiasis.[32]

Summary

Symptomatic cholelithiasis, or uncomplicated gallstone disease, is very common. Multiple risk factors exist and are associated with the balance of cholesterol, bile salts, and lecithin in the body. Biliary colic with otherwise normal examination findings and laboratory values and the findings of gallstones on ultrasound should alert the clinician to the likely diagnosis of symptomatic cholelithiasis. Although a small subset of patients may benefit from oral dissolution therapy, the gold standard for treatment is laparoscopic cholecystectomy. Additional avenues for medical management continue to be researched.

FUNCTIONAL DISORDERS OF THE BILIARY TRACT: BILIARY DYSKINESIA AND SPHINCTER OF ODDI DYSFUNCTION

Functional gastrointestinal disorders are defined by chronic or recurrent gastrointestinal symptoms that cannot be explained by structural or biochemical abnormalities. That is not to say that there are not physiologic abnormalities associated with functional disorders but that their presence may not coincide with symptoms or correction

with relief of symptoms.[33] Given the lack of structural or biochemical abnormalities, these disorders must be identified by the pattern of symptoms they cause. These symptoms cluster into recognizable syndromes with symptoms centered on various gastrointestinal organs. These recognizable syndromes have been defined by the Rome criteria.[34] The 3 types of functional biliary disorders based on Rome III diagnostic criteria are functional gallbladder disorder (FGD) and functional biliary or pancreatic sphincter of Oddi disorder (SOD) (**Box 1**).[35] Diagnosis is made through clinical evaluation and imaging studies, which evaluate gallbladder contractility and ejection fraction for FGD and pressure differentials through manometry for SODs. The Rome III criteria were developed to minimize invasive procedures, such as endoscopic retrograde cholangiopancreatography (ERCP) in those patients who do not meet the diagnostic criteria, thereby limiting associated complications to those invasive procedures.[36] The current gold standard in treatment is laparoscopic cholecystectomy and endoscopic sphincterotomy (ES), respectively.[37]

FGD

Functional gallbladder disorder is the term currently accepted by the Rome classification for gallbladder dyskinesia. FGD is a motility disorder initially caused by either metabolic abnormalities or a primary motility alteration.[36] Synonyms for FGD include various names, such as gallbladder spasm, acalculous biliary disease, gallbladder dyskinesia, and cystic duct syndrome.[38,39] Objective data using the radionuclide gallbladder ejection fraction (GBEF) aid in diagnosis and most patients' symptoms are relieved with cholecystectomy.[37]

Box 1
Rome III criteria. Functional gallbladder and sphincter of Oddi disorders

- Diagnostic criteria
  - Episodes of right upper quadrant pain or epigastric pain and ALL of the following:
    - Episodes lasting 30 min or longer
    - Recurrent symptoms occurring at different intervals (not daily)
    - The pain builds up to a steady level
    - The pain is moderate to severe enough to interrupt the patient's daily activities or lead to an emergency department visit
    - The pain is not relieved by bowel movements
    - The pain is not relieved by postural change
    - The pain is not relieved by antacids
    - Exclusion of other structural disease than would explain the symptoms
- Supportive criteria
  - The pain may present with one or more of the following
    - Associated nausea and vomiting
    - Radiates to the back and/or right infra-subscapular region
    - Awakens from sleep in the middle of the night

From Rome Foundation, Inc. Rome III diagnostic criteria for functional gastrointestinal disorders. Available at: http://www.romecriteria.org/criteria/. Accessed July 26, 2013.

Epidemiology

The true prevalence of FGD is unknown and varies per study. One large study reported the prevalence of biliary pain without stones to be about 2.4%.[12] Another Italian study evaluated biliary pain with normal transabdominal gallbladder ultrasound imaging in men and women and estimated the prevalence to be 8% and 21%, respectively.[40]

Pathophysiology

The true pathophysiology of FGD is unknown. The normal physiology of the gallbladder is regulated by neurohormonal mechanisms involving the vagus and splanchnic nerves and, most notably, the hormone cholecystokinin (CCK). The liver continuously secretes bile through the intrahepatic to the extrahepatic bile ducts. The sphincter of Oddi (SO) then aids in gallbladder filling and bile storage. The bile remains stored and concentrated in the gallbladder during the fasting state and then empties during the digestive phases. Vagus nerve (efferent fibers) stimulation and CCK release contracts the gallbladder, while splanchnic nerve stimulation relaxes the gallbladder. During the fasting state, nonpropulsive contractions also exist, likely to prevent bile stasis.[36] Abnormalities in any of these processes may be responsible for the symptoms observed.

Impaired gallbladder emptying, chronic inflammation, visceral hypersensitivity, and panenteric motility disorders have all been proposed as causes for FGD.[41] Impaired gallbladder emptying, or gallbladder hypokinesia/dyskinesia, may lead to supersaturation of bile with cholesterol monohydrate because of associated bile stasis.[42] Ineffective gallbladder contraction ultimately leads to a failure of gallbladder mixing and subsequent crystal formation, which then leads to chronic inflammation of the gallbladder wall. This theory was initially tested by Brugge and colleagues and reinforced by Velanovich, who studied patients with biliary-type pain, normal ultrasound imaging, and poor gallbladder emptying undergoing cholecystectomy. Intraoperative bile aspiration and postoperative pathologic abnormality were analyzed. Brugge illustrated that all those with preoperative crystals had chronic cholecystitis histologically. Velanovich reported 89% of patients without stones had crystals within their gallbladder walls and 94% of patients without stones had pathologic evidence of chronic cholecystitis. Both reports suggest acalculous gallbladder disease and dysmotility will eventually lead to gallstone formation and chronic inflammation.[43,44] However, some argue that the histologic changes are a cause, and not the effect, of poor gallbladder contractility.[42] Moreover, abnormal histology is not universal in patients with presumed FGD as studies report chronic inflammatory changes ranging from 44% to 100%.[45–47]

Clinical Presentation

The Rome III diagnostic criteria as listed in **Boxes 1** and **2**[35] define the clinical presentation of FGD. The criteria were developed by consensus and are not substantiated by any published evidence. The intent was to develop criteria to limit extensive investigations with invasive procedures and inappropriate endoscopic and surgical procedures.[36] They are generalizations that may not encompass every patient but should be used as a guideline when considering subjecting patients to potential harm.

Diagnostic Procedures

In the setting of biliary colic, other more common diagnoses, such as gastroesophageal reflux disease, irritable bowel syndrome, functional dyspepsia, and cholelithiasis, should be evaluated before considering FGD.[36] Abdominal ultrasonography is normal

Box 2
Rome III criteria. Functional gallbladder disorder

Diagnostic criteria

Must include ALL of the following:

Criteria for functional gallbladder and SOD

Gallbladder is present

Normal liver enzymes, conjugated bilirubin, and amylase/lipase

From Rome Foundation, Inc. Rome III diagnostic criteria for functional gastrointestinal disorders. Available at: http://www.romecriteria.org/criteria/. Accessed July 26, 2013.

in FGD. With that said, it is important to recognize the limitation of ultrasound in recognizing stones less than 3 to 5 mm in size and for stones or sludge within the common bile duct.[48] Upper gastrointestinal endoscopy is indicated once normal laboratory analysis and ultrasound imaging are obtained. Further evaluation with CCK and GBEF calculation is typically used as well.[49] Historically, the CCK provocation test was used but has fallen out of favor due to low sensitivity and specificity for FGD. Pain induced by CCK has been shown to be a function of the method of infusion not underlying disease.[50]

Endoscopic evaluation is used for FGD and other causes and for more specific testing to include bile sampling. Endoscopy can aid in the elimination of gastric or duodenal pathologic abnormality. Endoscopic bile sampling and EUS can aid in the detection of small gallbladder or bile duct stones. EUS allows for improved sensitivity for identifying small gallstones when compared with transabdominal ultrasound. Bile sampling can be done with standard endoscopy taking a sample from near the ampulla or directly from the bile duct by ERCP. The bile sample is used to evaluate for microlithiasis. To increase the sensitivity for microlithiasis, intravenous CCK is injected, and a sample of bile is obtained that has not been diluted by pancreatic and duodenal fluids. Cholesterol crystals identified in gallbladder bile is strongly associated with small gallbladder calculi and these patients typically benefit from cholecystectomy.[37] A prospective study by Dahan and colleagues[51] in which EUS and microscopic bile examination were compared reported a statistically significant higher sensitivity in the diagnosis of cholecystolithiasis by EUS, 97%, than by bile microscopy, 67%. Specificities were comparable. Furthermore, if both were negative, the likelihood of cholecystolithiasis was very low. Thorboll and colleagues[52] evaluated EUS as a solitary diagnostic method in patients with biliary colic and normal ultrasonography. EUS detected microlithiasis in 52.4% of patients with postoperative pathologic confirmation in 87% of patients. Another study by Mirbagheri and colleagues[53] confirmed the importance of EUS in the diagnosis of microlithiasis for patients with normal ultrasonography.

The functional assessment of gallbladder emptying by cholescintigraphy has become the test of choice for the evaluation of suspected FGD.[35,49] The hepatobiliary iminodiacetic acid (HIDA) cholecystokinin cholescintigraphy (CCK-CS) uses a radioactive biomarker, a gamma camera, and computer analysis to aid in estimating GBEF.[37] Technetium-99m-labeled iminodiacetic acid is administered, which has a high affinity for hepatic uptake and is readily excreted into the biliary tract and concentrated in the gallbladder. A fatty meal is ingested or CCK is administered to stimulate gallbladder emptying and serial observations of net change in gallbladder activity are reported as GBEF.[36]

A low GBEF is considered diagnostic of impaired gallbladder function. However, the accuracy of CCK-HIDA and GBEF is not without limitations. There is debate as to the dose, infusion rate, when to assess emptying, and what constitutes a low GBEF.[49] A low GBEF, or positive HIDA scan, is not specific for FGD. Many medical conditions to include diabetes, celiac disease, pregnancy, or irritable bowel syndrome, as well as many medications such as opioids, oral contraceptives, calcium channel blockers, benzodiazepines, and histamine-2-receptor antagonists, can cause low GBEF.[42] Regarding the controversy concerning the appropriate dose of CCK and infusion rate as well as timing of GBEF calculation, the pivotal study of GBEF by Yap and colleagues[54] used a CCK dose of 0.02 μg/kg/min infused over 45 minutes with a GBEF calculated at 60 minutes. They reported a normal GBEF of greater than 40% based on 40 asymptomatic patients. Multiple studies have evaluated infusion dose, rates, and times and GBEF since then. Essentially, shorter CCK infusion times are unreliable for predicting GBEF and longer infusion times of 30 to 60 minutes have less variation, which allows for the calculation of a normal GBEF to be $\geq$40%.[49] Ziessman and colleagues[55] then published a multicenter investigation to determine optimal infusion methods as well as establishment of normal GBEF values. The findings from this study prompted the delineation of a standard methodology for CCK-CS. In 2012 a multispecialty consensus panel published recommendations for CCK-CS to standardize a protocol and improve patient care. Current recommendations are to infuse 0.02 μg/kg of sincalide (CCK analogue) over 60 minutes. The panel also defined a normal GBEF of $\geq$38%. Finally, the panel also recommends a large, multicenter, randomized, prospective trial to establish the utility of CCK-CS in the diagnosis of FGD[56]; this is similar to the current Rome III recommendation of an abnormal ejection fraction of less than 40% after a continuous infusion of CCK greater than 30 minutes.[57]

Treatment and Outcomes

FGD or biliary dyskinesia has been commonly treated with cholecystectomy. Medical therapy is available, but has not been compared directly with cholecystectomy in a trial. Medications used include spasmolytics, choleretics, cholekinetics, and psychotropic drugs.[58] There is a single randomized trial examining surgery versus nonoperative treatment of FGD. Yap and colleagues[54] found a 91% symptomatic relief in the surgical group at a mean follow-up for 34 months and no patient with resolution of symptoms in the nonoperative group. Unfortunately, the trial accrued only 21 patients and a larger randomized trial has not been repeated. Two recent meta-analyses examined the effectiveness of surgical therapy for biliary dyskinesia. Ponsky and colleagues[59] evaluated 274 patients in 5 studies with biliary dyskinesia, as defined by biliary colic, without gallstones on ultrasound and GBEF less than 40%. Two hundred patients underwent cholecystectomy and 74 were treated nonoperatively. Symptomatic relief was reported in 98% of patients in the surgical group versus 32% in the nonoperative group. Mahid and colleagues[60] found similar results. The authors evaluated 10 studies with 462 patients and again compared cholecystectomy with nonoperative treatment of HIDA-positive biliary dyskinesia. Surgical treatment was 15-fold more likely than medical treatment to result in symptom improvement for patients without gallstones, with biliary colic, and a positive HIDA scan. Although available studies indicate generally good outcomes for cholecystectomy for FGD, the evidence is based on a single very small randomized trial and a series of chart reviews. Several authors have called for larger randomized controlled trials with some kind of active intervention for the nonoperative arm.[61,62] Further research is also supported by the estimate that approximately 30% of patients who undergo cholecystectomy for biliary dyskinesia will continue to have symptoms after surgery. Postprandial nausea and

vomiting have been reported as a poor prognostic factor for surgery and a lower quality of life postoperatively, possibly due to a global gastrointestinal motility disorder.[63]

Summary

FGD is a diagnosis of exclusion whereby the patient experiences biliary colic in the absence of gallstones, with decreased GBEF. The functional assessment of the gallbladder by CCK-HIDA has become the most widely used imaging test, which has recently been standardized to improve patient evaluation and management. A single small randomized trial and several meta-analyses have shown symptomatic benefit with cholecystectomy for FGD; however, larger randomized trials would be beneficial to try and reproduce results, as some reports state approximately 30% of patients' symptoms will continue postoperatively.

FUNCTIONAL SOD

SOD is the term used for motility abnormalities of the SO associated with biliary and pancreatic pain, elevation of liver or pancreatic enzymes, common bile duct dilation, and recurrent episodes of pancreatitis.[36] SOD is one of the functional gastrointestinal disorders. Rome III diagnostic criteria defines both a biliary and a pancreatic SOD.[35] SOD is divided further into 3 categories (I, II, III) based on symptoms, radiologic findings, and serologic findings and these categories for biliary SOD are based on the Milwaukee criteria (**Table 1**).[64] SOD can occur with an intact gallbladder; however, most data are based on patients with continued symptoms following cholecystectomy and very few gastroenterologists will offer treatment, ES, before cholecystectomy.[65]

Epidemiology

SOD is estimated to affect 14% of patients with right upper quadrant pain after cholecystectomy and less than 1% of patients with an in situ gallbladder.[66,67] Biliary SOD

Table 1
Milwaukee criteria related to the frequency of abnormal sphincter of Oddi manometry and pain relief by biliary sphincterotomy

Patient Group Classification	Frequency of Abnormal Sphincter Manometry	Probability of Pain Relief by Sphincterotomy if Manometry		Manometry Before Sphincter Ablation
		Abnormal	Normal	
Biliary I (%) Biliary-type pain Abnormal AST or ALP > ×2 normal Delayed drainage of ERCP contrast from the biliary tree >45 min Dilated CBD >12 mm diameter	75–95	90–95	90–95	Unnecessary
Biliary II (%) Biliary-type pain Only 1 or 2 of the above criteria	55–65	85	35	Highly recommended
Biliary III (%) Only biliary-type pain	25–60	55–65	<10	Mandatory

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; CBD, common bile duct.
From Cheon YK. How to interpret a functional or motility test—sphincter of Oddi manometry. J Neurogastroenterol Motil 2012;18:211–7.

is more common in women than men and is associated with a high incidence of disability, health care costs, and work absence.[68] As in FGD, other possible causes of the pain must be excluded, including costochondritis, nerve injury at trochar site, gastroparesis, irritable bowel syndrome, peptic ulcer disease, and other intra-abdominal causes.[66] Most patients present with the postcholecystectomy syndrome, persistent, right upper quadrant abdominal pain following gallbladder removal. Thus, the more common causes and complications related to the surgery, such as retained stones, bile leak, or bile duct injury, must also be ruled out.[69] Pancreatic SOD is associated with idiopathic recurrent acute pancreatitis (RAP). The estimated prevalence of pancreatic SOD is approximately 30% in patients with unexplained acute pancreatitis; however, that number ranges from 15% to 72% in studies.[70–74]

Pathophysiology

Anatomically, the SO is at the junction of the biliary and pancreatic ducts in the duodenum. Dysfunction can occur in either the biliary or the pancreatic portion or both. One study of more than 300 patients with pancreaticobiliary pain reported abnormal pancreatic sphincter pressure in 19%, abnormal biliary basal sphincter pressure in 11%, and combined biliary and pancreatic pressure elevations in 31%.[75] More than 100 years ago, Rugero Oddi first identified the sphincter and was also the first to write about possible dysfunction leading to symptoms.[37] Then, in 1937, Boyden described the anatomy of the SO in great detail.[76] The human SO has a well-defined musculature, is approximately 10 mm in length, and has intramural and extramural segments. Three relatively discrete zones of muscle are identified as minisphincters called the sphincter choledochus, the sphincter ampulla, and the sphincter pancreaticus (Fig. 2). The ampulla is a common channel formed by the junction of the pancreatic and common bile ducts and drains through the papilla of Vater into the duodenum.[77] The SO is independent from the duodenum with differing myoelectric and contractile patterns. The basal pressure of the SO ranges from 10 to 15 mm Hg with superimposed forceful contractions of up to 150 mm Hg.[78] The main functions of the SO include regulation of flow into the duodenum, reflux prevention from the duodenum to the bile and pancreatic duct, and gallbladder filling.[79] During fasting, most of the bile is diverted toward the gallbladder by resistance of the SO, whereas during the

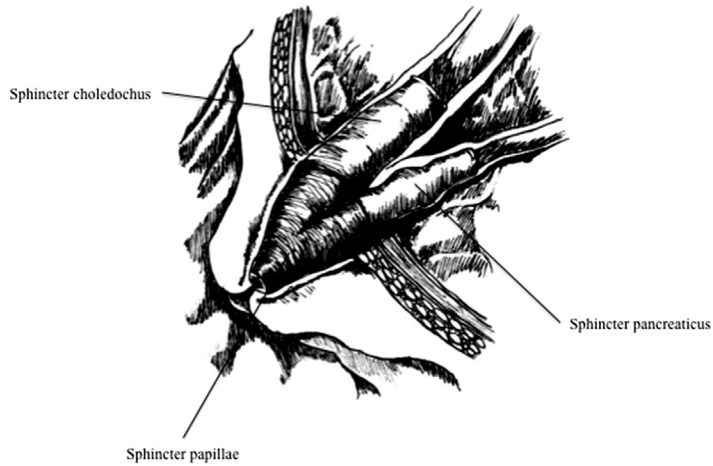

Fig. 2. The sphincter of Oddi. (*Courtesy of* Robert B. Lim, MD Honolulu, HI.)

digestive phase, the gallbladder contracts and the SO relaxes, allowing release of bile into the duodenum for fat digestion and absorption. CCK leads to a coordinated contraction of the gallbladder and relaxation of the SO and duodenum, which ultimately leads to bile discharge into the duodenum. When the SO is severed, such as in sphincterotomy, there will be reflux of air and bile into the common bile duct.[78]

Clinical Presentation

The Rome III criteria also have established a set of guidelines for the diagnosis of functional biliary or pancreatic SOD. As shown in **Boxes 1**, **3**, and **4**, both disorders must include the criteria for functional gallbladder and SO disorders, with normal amylase and lipase for biliary SOD or elevated amylase and lipase for pancreatic SOD. Biliary SOD patients typically present with biliary-type pain in the epigastrium or right upper quadrant with modifying factors as described previously. Biliary SOD is most commonly considered in the setting of postcholecystectomy pain. Pancreatic SOD patients have recurrent episodes of epigastric pain similar to biliary SOD patients, but radiation to the back can occur.[35] In addition, most patients with pancreatic SOD will present with recurrent episodes of pancreatitis.[80] In the absence of common causes of pancreatitis (stones, alcohol, triglycerides, pancreatic divisum), idiopathic recurrent pancreatitis or pancreatic SOD can be considered.[35] SOD is a notable disorder in the post-gastric bypass population and should be considered in these patients with biliary pain following cholecystectomy. A small series showed good relief of symptoms in post-gastric bypass patients with SOD who underwent transduodenal sphincterotomy.[81]

Diagnostic Procedures

Sphincter of Oddi manometry (SOM) is the gold standard for the diagnosis of SOD. Other imaging studies such as ultrasound, CCK-HIDA, or magnetic resonance cholangiopancreatography are used to evaluate for other causes. Other indirect tests have been used to avoid the invasive means of manometry; however, none of those studies produce the results that manometry can achieve through direct SO measurement.[36] Direct pressure measurements are obtained during ERCP in which a pressure catheter is inserted through the biopsy channel of the endoscope into the biliary or pancreatic duct. SOM has a significant risk of post-ERCP pancreatitis, which is higher than the risk with ERCP performed for other indications. Post-ERCP pancreatitis rates range from 10% to 40% in patients suspected of having SOD.[65,82] Patients with Milwaukee

Box 3
Rome III criteria. Functional biliary sphincter of Oddi disorder

Diagnostic criteria

- Must include BOTH of the following:
  - Criteria for functional gallbladder and SOD
  - Normal amylase/lipase

Supportive criteria

- Elevated serum transaminases, alkaline phosphatase, or conjugated bilirubin temporarily related to at least 2 pain episodes

From Rome Foundation, Inc. Rome III diagnostic criteria for functional gastrointestinal disorders. Available at: http://www.romecriteria.org/criteria/. Accessed July 26, 2013.

Box 4
Rome III criteria. Functional pancreatic sphincter of Oddi disorder

Diagnostic criteria

Must include BOTH of the following:

Criteria for functional gallbladder and SOD

Elevated amylase/lipase

From Rome Foundation, Inc. Rome III diagnostic criteria for functional gastrointestinal disorders. Available at: http://www.romecriteria.org/criteria/. Accessed July 26, 2013.

classification SOD III are at the highest risk.[83] Recently placement of a pancreatic duct stent in patients suspected of having SOD has been shown to reduce the risk of post-ERCP pancreatitis.[84] SOM measurements include basal sphincter pressure, intraductal pressure, and phasic wave parameters.[75] Guelrud and colleagues[85] studied 50 asymptomatic healthy volunteer subjects to detail the characteristics of SO motor function and to help establish normal values. Findings are summarized in **Table 2**. Elevated basal sphincter pressures higher than 40 mm Hg are currently the gold standard to diagnose SOD.[66] However, other manometry abnormalities may include increased amplitude or frequency of phasic waves, paradoxic response to CCK, and increased quantity of retrograde waves.[36] Several factors, such as manometry technique and medications (nitrates, calcium channel blockers, anticholinergics, phosphodiesterase type 5 inhibitors, narcotics), can affect SO pressure and motility.[75]

SOM is not recommended for biliary type I SOD patients by many authors based on good results from ES independent of manometry findings.[66,72,86,87] Results of ES are not as universally good for biliary type II and particularly type III patients (see **Table 1**).[64] Complications for ES are also higher for patients with normal SOM, more frequently seen in biliary type II and most frequently in type III patients.[83] Based on this, SOM is recommended for biliary type II patients and is mandatory for all type III patients if sphincter ablation is considered.[66] In cases of suspected biliary SOD, SOM is typically only performed for the biliary sphincter.[88] However SOD may involve the biliary, the pancreatic, or both sphincters in patients with pancreaticobiliary pain and recurrent idiopathic pancreatitis.[89,90] Therefore manometry of both the biliary and the pancreatic sphincters is recommended by some authors in patients suspected of SOD undergoing SOM.[57,88] Particular consideration should be given in cases of type III SOD undergoing SOM because of the difficulty differentiating biliary

Table 2
Abnormal values for endoscopic SOM

Suggested Standard for Abnormal Values for Endoscopic SOM	
Basal sphincter pressure	>35 mm Hg
Phasic contractions	
Amplitude	>220 mm Hg
Duration	>8 s
Frequency	>10/min

Values were obtained by adding 3 SD to the mean.

From Guelrud M, Mendoza S, Rossiter G, et al. Sphincter of Oddi manometry in healthy volunteers. Dig Dis Sci 1990;35:38–46; with permission.

from pancreatic pain and generally poorer response to biliary ES (BES). Patients with failure to resolve symptoms after BES should also be considered for pancreatic SOM because up to 90% of these patients will have pancreatic SOD.[90] SOM is indicated in those with previously normal SOM studies but persistent symptoms consistent with SOD. A study of more than 5000 patients evaluated the frequency of SOD in persistently symptomatic patients with previously normal SOM studies, to determine if the short-term manometry recordings during ERCP reflect the 24-hour pathophysiology of the sphincter. Of 1037 patients with normal SOM studies, 30 underwent repeat ERCP with SOM for persistent symptoms and 60% of those patients were then diagnosed with SOD. Thus, repeat SOM may be warranted in patients with persistent debilitating symptoms and a high index of suspicion for SOD in which previous SOM is normal.[91]

Other potential diagnostic procedures are also available for further evaluation of SOD. Quantitative cholescintigraphy with a fatty meal or CCK administration can be used to evaluate for SOD. In postcholecystectomy patients, the flow of bile from the liver into the duodenum is primarily regulated by the SO and patients with SOD will show marked delay in transit into the duodenum.[92] However, precise criteria to define an abnormal study remain controversial. The hilum to duodenum transit time of greater than 10 minutes and the duodenal appearance time greater than 20 minutes are the most frequently used in studies.[93] In addition to the controversy over criteria, studies show varying results regarding correlation to SOM and no studies show correlation with outcome after ES. Where correlation occurs, it is most commonly with type I patients in whom it is frequently not necessary.[66,94,95] In patients with intact gallbladders, the criteria for diagnosis of SOD are based on delayed biliary visualization, intrahepatic biliary prominence, and biliary-bowel transit time.[96] The injection of secretin with subsequent measurement of the main pancreatic duct diameter has been studied in comparison with SOM. Ultrasound or magnetic resonance pancreatography has been used, but has not been shown to correlate with manometry or to predict outcomes.[97–99] Morphine-neostigmine provocation has also been suggested, but the low sensitivity and specificity have been disappointing.[100]

Treatment for Biliary SOD

The most well-known classification system for SOD was proposed by Hogan and Geenen[101] in 1988 and is known as the Milwaukee classification. Three groups of patients were identified and classified based on symptoms and laboratory or imaging abnormalities to include ERCP biliary drainage times. This classification has been revised by the Rome III project to use noninvasive methods, ultrasonographic measurement of the bile duct, over ERCP drainage times and can be seen in **Table 3**. Type I biliary SOD is also referred to as benign SO stenosis and type II and type III biliary SOD are also referred to as SO dyskinesia. SO dyskinesia is an intermittent symptomatic disease; thus, short-time SOM may not capture the pathologic abnormality.[102]

Sphincter ablation is the treatment for SOD. The traditional surgical approach is transduodenal biliary sphincteroplasty with a transampullary septoplasty (**Fig. 3**). The surgical approach has been replaced by endoscopic therapy in most instances and is based on decreased morbidity, mortality, and cost. Surgical therapy is reserved for endoscopic failures and in cases where endoscopic methods are not technically possible.[88]

It is generally accepted that type I biliary SOD patients have true papillary stenosis and should undergo ES without manometry; this is based on reported relief of symptoms after ES ranging from 90% to 95% regardless of manometry results, which are normal in 14% to 35% of cases.[86,103,104] Some argue that occult biliary microlithiasis

Table 3
Classic and revised classification for SOD

	Type	Classic	Revised
Biliary	I	Abnormal hepatic enzymes on 2 occasions + dilated CBD + delayed drainage >45 min	Abnormal hepatic enzymes + dilated CBD
	II	1 or 2 of abnormal hepatic enzymes ×2, dilated CBD, delayed drainage >45 min	Either abnormal hepatic enzymes or dilated CBD
	III	No laboratory or imaging abnormalities	
Pancreatic	I	Abnormal pancreatic enzymes on 2 occasions + dilated PD + delayed drainage >8 min	Abnormal pancreatic enzymes + dilated PD
	II	1 or 2 of abnormal pancreatic enzymes ×2, dilated PD, delayed drainage >8 min	Either abnormal pancreatic enzymes or dilated PD
	III	No laboratory or imaging abnormalities	

Biliary, all patients present with biliary type pain; Pancreatic, all patients present with recurrent pancreatitis or typical pancreatic pain.

Abbreviations: CBD, common bile duct; PD, pancreatic duct.

Adapted from Peterson BT. Sphincter of Oddi dysfunction, part 2: evidence-based review of the presentations, with "objective" pancreatic findings (types I and II) and of presumptive type III. Gastrointest Endosc 2004;59:670–87.

is actually the same clinical entity as type I SOD because they have similar clinical presentations and both show clinical improvement with endoscopic treatment.[105]

Type II SOD represents a functional sphincter disturbance. Patients should undergo SOM and those with elevated biliary sphincter pressures typically undergo ES for treatment.[66] The recommendation is based on 2 randomized controlled trials that showed improvement with ES for patients with elevated basal pressures. However several retrospective studies did not find symptom improvement was associated with abnormal SOM.[106] Geenen and colleagues[64] randomized 47 patients with type II SOD to ES or sham sphincterotomy. After randomization but before ES, SOM was performed. At 1-year follow-up ES resulted in clinical improvement in 10 of 11 patients who had elevated sphincter pressures versus improvement in only 3 of 12 patients in the sham group. Seven patients in the sham sphincterotomy group with elevated sphincter pressures crossed over and underwent ES. At 4-year follow-up, 17 of 18 patients with initially elevated sphincter pressures demonstrated symptom improvement after ES. Patients with normal SOM had no benefit from ES compared with sham sphincterotomy. Toouli and colleagues[107] randomized 81 patients with types I and II SOD to ES or sham sphincterotomy. SOM classified each into 3 categories: elevated basal pressures, dyskinesia (phasic contraction abnormalities), and normal. At 3 and 24 months, symptoms improved in 11 of 13 patients with elevated basal pressures treated by ES versus only 5 of 13 in the sham group. Results between ES and sham did not differ for the dyskinesia or normal groups. A recent review of available studies showed long-term symptom relief for type II SOD in up to 79% of patients.[66]

Several reports have evaluated ES for the subset of type III SOD and results are mixed. Botoman and colleagues[108] found symptom improvement at 3 years of 56% for SOD type III patients with elevated basal biliary sphincter pressures. Freeman and colleagues[82] found 62% symptom improvement at 2 years in SOD type III patients irrespective of SOM findings. Finally Wehrmann and colleagues[109] found only 8% of SOD type III patients with elevated basal biliary sphincter pressures had symptom

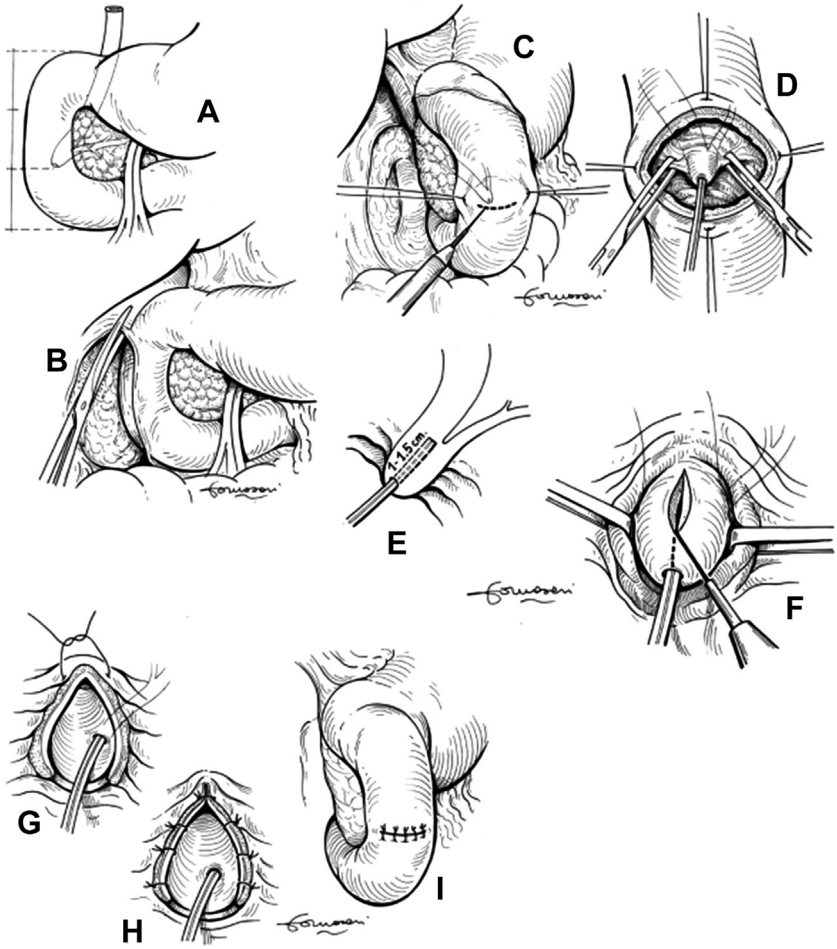

Fig. 3. The ampulla of Vater position in relation to the (*A*) second duodenal loop and (*B*) duodenal mobilization. Incision of the duodenum after the wall, opposite the ampulla of Vater, is exposed by (*C*) rotating the mobilized duodenum to the left; the papilla is exposed and (*D*) a grooved director is introduced into its proximal end. Following the guidance of the (*E*) grooved director, the (*F*) papilla is incised for 1 to 1.5 cm. After papillotomy, (*G*) sinus probe has been introduced into the proximal end of the Wirsung duct. Suture of the medial aspect of papillotomy (*H*) is completed. (*I*) Duodenal closure. (*From* Miccini M, Amore Bonapasta S, Gregori M, et al. Indications and results for transduodenal sphincteroplasty in the era of endoscopic sphincterotomy. Am J Surg 2010;200:247–51; with permission.)

improvement at 2.5 years after ES. Given the variations in outcomes among studies of ES in type III SOD, ES is only considered after all other potential causes have been evaluated and the patient has failed medical management. At this point SOM can be considered and ES, if basal biliary sphincter pressure is elevated. Medical therapy in type III SOD has been shown to be effective in decreasing symptoms in 71% of patients.[110] Furthermore, symptoms may resolve spontaneously in up to 69.8% of patients with type III disease.[66]

Medical therapy should be considered in all type III SOD and in mild type II SOD, before considering sphincterotomy. Because the SO is a smooth muscle sphincter,

medical therapy has been aimed at smooth muscle relaxation. Calcium channel blockers and nitrates have been the subject of investigation. Sublingual nifedipine and nitrates have been shown to reduce basal sphincter pressures in healthy volunteers as well as in symptomatic patients.[111,112] Nifedipine is the most well-studied medical therapy and has been shown to be effective in symptomatic improvement of patients with documented SOD by manometry. Khuroo and colleagues[113] found in a prospective, randomized, placebo controlled crossover trial that 75% of patients with manometrically documented type II and III SOD had improvement in symptoms and Emergency Room visits with use of nifedipine and oral analgesics over the 12-week treatment period. Sand and colleagues[114] found similar findings over a 16-week trial in type II SOD patients. However, associated vasodilator effects such as headaches, flushing, and dizziness can limit long-term use and the studies with nifedipine have short follow-up. Vardenafil, a phosphodiesterase type 5 inhibitor, has been shown to significantly reduce mean basal sphincter pressure and mean phasic amplitude in patients undergoing SOM, but has not been evaluated for clinical response.[115] Lower levels of serum motilin and gastrin have been shown to be associated with hypomotility of the SO.[116] Trimebutine is a medication with antimuscarinic effects and is marketed for treatment of irritable bowel syndrome and other gastrointestinal disorders. A recent study treated 59 patients with SOD for 1 year with Trimebutine and clinically re-evaluated each patient after 30 months. At the end of follow-up, 62% of patients showed more than 50% improvement with medical management alone. The improvement rate was no different in patients who ultimately underwent ES after failure of medical management (64%).[117] Although promising, further trials with long-term data are needed to evaluate long-term effectiveness of medical SOD management. With that said, given the relative safety of medical therapy and the non-life-threatening nature of SOD, strong consideration should be given to initial treatment of all type III SOD and mildly symptomatic type II SOD patients before ES.[118]

Treatment for Pancreatic SOD

A classification system similar to the Milwaukee classification for biliary SOD has also been developed for pancreatic SOD (**Box 5**). The current recommendation for

Box 5
Modified classification of pancreatic type SOD

Type I

- Pancreatic-type pain
- Amylase/lipase >1.5–2 times normal
- Pancreatic duct diameter >6 mm in head or >5 mm in body

Type II

- Pancreatic-type pain and 1 of the following:
- Amylase/lipase >1.5–2 times normal
- Pancreatic duct diameter >6 mm in head or >5 mm in body

Type III

- Pancreatic-type pain only

From Prajapati DN, Hogan WJ. Sphincter of Oddi dysfunction and other functional biliary disorders: evaluation and treatment. Gastroenterol Clin North Am 2003;32:601–18.

pancreatic SOD with elevated basal pressures on SOM is ES. Many authors think complete division of the biliary and pancreatic sphincters is necessary, and the septum is required.[36,57,88,118] Toouli and colleagues[119] examined patients with idiopathic pancreatitis and found treatment aimed at the biliary sphincter failed in 10 of 16 patients, whereas therapy directed at the pancreatic sphincter was successful in 23 of 26 patients. Long-term follow-up was significant for no further episodes of pancreatitis in more than 90% of patients.[120] Park and colleagues[121] examined 313 patients with pancreaticobiliary pain and abnormal pressures in the biliary, pancreatic, or both sphincters. All patients underwent sphincterotomy of both sphincters (dual endoscopic sphincterotomy [DES]) at a single setting. Reintervention rates were then examined. There was no difference in reintervention rates between type II and type III SOD. The patient's reintervention rate was compared with historical controls that underwent only BES. Patients with an isolated abnormal pancreatic sphincter underwent reintervention at a significantly lower rate than historical controls. Patients with an isolated abnormal biliary sphincter or abnormality of both sphincters had similar reintervention rates. In the only randomized trial for RAP, Cote and colleagues[122] randomized 69 patients with idiopathic pancreatitis and elevated pancreatic sphincter pressures to DES versus BES. Another 20 patients with idiopathic pancreatitis and normal pancreatic sphincter pressures were randomized to BES or sham sphincterotomy. At a median of 78 months follow-up rates of RAP were significantly higher for the patients with abnormal SOM than patients with normal SOM. The rates for RAP in the DES were similar to the BES for patients with abnormal SOM and rates were similar between sham sphincterotomy and BES in the normal SOM group. The one caveat to this study is the percentage of patients in the BES group with abnormal biliary SOM was significantly higher than the DES group. The results of this randomized trial differ from most retrospective studies previously showing benefit to pancreatic sphincterotomy. Given these results and the risks associated with pancreatic sphincterotomy, it seems reasonable to begin with BES, particularly if biliary SOM is abnormal.

Summary

Functional disorders of the SO represent a group of disorders that are incompletely defined with variable responses to treatment. The SOD classification system is based on anatomy, symptoms, and objective findings and, although imperfect, continues to be the best way to group these disorders to aid in further investigation and management. Noninvasive diagnostic testing should be further investigated, but current results lack sensitivity or specificity to guide therapy. Type I SOD should be managed by ES without SOM. Type II SOD should have a trial of medical therapy before subjecting to risks of SOM. In patients where medical management fails, and with appropriate discussion of risk and benefits, SOM can be done and ES for abnormal results. Type III disease is pain alone without abnormal laboratory or imaging findings. Type III SOD should have extensive investigation for alternate diagnosis and be treated with medical therapy. Given the variability of response to ES in studies, the relatively high response to medical therapy, and the risks of SOM, SOM and ES for an abnormality should be used after exhausting all other avenues. Patients with pancreatic SOD and elevated SOM should undergo ES. Pancreatic SOD type III should be treated the same as biliary type III and likely are the same group.

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