Sphincter of Oddi Dysfunction: Diagnosis and Treatment

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Introduction

Since its original description by Ruggero Oddi in 1887, the sphincter of Oddi (SO) has been the subject of much study and controversy. Its very existence as a distinct anatomic or physiologic entity has been disputed. Hence, it is not surprising that the clinical syndrome of sphincter of Oddi dysfunction (SOD) and its therapy are controversial areas [1]. Nevertheless, SOD is commonly diagnosed and treated by physicians. This section reviews the anatomy and physiology of the SO, clinical presentations, and methods to diagnose and treat SOD.

Definition

SOD refers to an abnormality of SO contractility. It is a benign, noncalculous obstruction to flow of bile or pancreatic juice through the pancreaticobiliary junction, i.e., the sphincter of Oddi. SOD may be manifested clinically by pancreaticobiliary pain, pancreatitis, or deranged liver function tests. It is actually made up of two entities. SO dyskinesia refers to a primary motor abnormality of the SO which may result in a hypotonic sphincter but more commonly, a hypertonic sphincter. In contrast, SO stenosis refers to a structural alteration of the sphincter, probably from an inflammatory process with subsequent fibrosis. Because it is often impossible to distinguish patients with SO dyskinesia from those with SO stenosis, the term SOD has been used to incorporate both groups of patients. In an attempt to deal with this overlap in etiology, and also to determine the appropriate utilization of SO manometry (SOM), a clinical classification system has been developed for patients with suspected SOD [2] (Hogan-Geenen SOD classification system; Table 1) based on clinical history, laboratory results, and ERCP findings.

A variety of less accurate terms are listed in the medical literature to describe this entity such as papillary stenosis, ampullary stenosis, biliary dyskinesia, and post-cholecystectomy syndrome (even though SOD may occur with the gallbladder intact).

Anatomy, Physiology and Pathophysiology

The sphincter of Oddi is a small complex of smooth muscles surrounding the terminal common bile duct, main (ventral) pancreatic duct (of Wirsung), and the common channel (ampulla of Vater), when present. It has both circular and figure-8 components. The high-pressure zone generated by the sphincter is variably 4-10 mm. in length. Its role is to regulate bile and pancreatic exocrine juice flow and to prevent duodenum-to-duct reflux (i.e., maintain sterile intraductal environment). The SO possesses both a variable basal pressure and phasic contractile activity. The former appears to be the predominant mechanism, regulating outflow of pancreaticobiliary secretion into the intestine. Although phasic SO contractions...
may aid in regulating bile and pancreatic juice flow, their primary role appears to be maintaining a sterile intraductal milieu. Sphincter regulation is under both neural and hormonal control. Phasic wave activity of the sphincter is closely tied to the migrating motor complex (MMC) of the duodenum. Innervation of the bile duct does not appear to be essential as sphincter function has been reported to be preserved following liver transplantation [3]. Although regulatory processes vary among species, cholecystokinin and secretin appear to be most important in causing sphincter relaxation while nonadrenergic, noncholinergic neurons which at least in part transmit vasoactive intestinal peptide (VIP) and nitric oxide also relax the sphincter [4]. The role of cholecystectomy in altering these neural pathways needs further definition. Luman and colleagues [5] reported that cholecystectomy, at least in the short-term, suppresses the normal inhibitory effect of pharmacological doses of CCK on the sphincter of Oddi. However, the mechanism of this effect is unknown.

Wedge specimens of the SO obtained at surgical sphincteroplasty from SOD patients, show evidence of inflammation, muscular hypertrophy, fibrosis or adenomyosis within the papillary zone in approximately 60% of patients [6]. In the remaining 40% with normal histology, a motor disorder is suggested. Less commonly, infections with Cytomegalovirus or Cryptosporidium, as may occur in AIDS patients, or Strongyloides have caused SOD.

How does SOD cause pain? From a theoretical point of view, abnormalities of the SO can give rise to pain by, impeding the flow of bile and pancreatic juice resulting in ductal hypertension, ischemia arising from spastic contractions, and “hypersensitivity” of the papilla. Although unproven, these mechanisms may act alone or in concert to explain the genesis of pain.

**Epidemiology**

SOD may occur in pediatric or adult patients of any age; however, patients with SOD are typically middle-aged females [7]. A survey on functional gastrointestinal disorders confirmed that SOD affects females more frequently than males and indicated a high association with work absenteeism, disability, and healthcare use [8]. Although SOD most commonly occurs after cholecystectomy, it may be present with the gallbladder in situ. The frequency of manometrically documented

<table>
<thead>
<tr>
<th>Patient group classifications</th>
<th>Approximate frequency of abnormal sphincter manometry</th>
<th>Probability of pain relief by sphincterotomy if manometry:</th>
<th>Manometry before sphincter ablation</th>
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<tbody>
<tr>
<td><strong>Biliary I</strong></td>
<td>75-95%</td>
<td>90-95%</td>
<td>90-95%</td>
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<tr>
<td>Patients with biliary-type pain, abnormal SGOT or alkaline phosphatase &gt;2 x normal documented on two or more occasions, delayed drainage of ERCP contrast from the biliary tree &gt;45 minutes, and dilated CBD &gt;12 mm diameter</td>
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<tr>
<td><strong>Biliary II</strong></td>
<td>55-65%</td>
<td>85%</td>
<td>35%</td>
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<tr>
<td>Patients with biliary-type pain but only one or two of the above criteria</td>
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<tr>
<td><strong>Biliary III</strong></td>
<td>25-60%</td>
<td>55-65%</td>
<td>&lt;10%</td>
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<td>Patients with only biliary-type pain and no other abnormalities</td>
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SOD in patients prior to cholecystectomy has received limited study. Guerrud and colleagues [9] studied 121 patients with symptomatic gallstones and a normal common bile duct diameter (by transcutaneous ultrasound) by SOM prior to cholecystectomy. An elevated basal sphincter pressure was found in 14 patients (11.6%). SOD was diagnosed in 4.1% of patients with a normal serum alkaline phosphatase (4 of 96) and in 40% with an elevated serum alkaline phosphatase (10 of 25). Ruffolo et al. evaluated 81 patients with symptoms suggestive of biliary disease but normal ERCP and no gallbladder stones on transcutaneous ultrasound by scintigraphic gallbladder ejection fraction and endoscopic SOM [10]. Fifty-three percent of patients had SOD and 49% had an abnormal gallbladder ejection fraction. SOD occurred with a similar frequency in patients with an abnormal gallbladder ejection fraction (50%) and a normal ejection fraction (57%).

Post-cholecystectomy pain resembling the patient's preoperative biliary colic occurs in at least 10-20% of patients [11]. The frequency of diagnosing SOD in reported series varies considerably with the patient selection criteria, the definition of SOD utilized, and the diagnostic tools employed. In a British report, Sphincter of Oddi dysfunction was diagnosed in 9% of 451 consecutive patients being evaluated for post cholecystectomy pain [12]. Roberts-Thomson evaluated 431 similar patients and found SOD in 11%. In a subpopulation of such patients with a normal ERCP (except dilated ducts in 28%) and recurrent pain of more than 3-month duration, SOD was diagnosed in 68% [13]. Sherman and colleagues used SOM to evaluate 115 patients with pancreaticobiliary pain with and without liver function test abnormalities [14]. Patients with bile duct stones and tumors were excluded from analysis. Fifty-nine of 115 patients (51%) had an abnormal basal sphincter of Oddi pressure greater than 40 mmHg. These patients were further categorized by the Hogan-Geenen SOD classification system (Table 1). The frequency of abnormal manometry was 86%, 55% and 28%, for Type I, II and III patients respectively. These abnormal manometric frequencies are very similar to those reported by others for Type I and Type II patients [15, 16]. In Type III patients, the finding of an abnormal basal sphincter pressure has varied from 12-55% [17]. As noted, patient selection factors may be one explanation for this great variability.

SOD can involve abnormalities in either the biliary sphincter, pancreatic sphincter, or both. The true frequency of SOD would then depend on whether one or both sphincters were studied. To fully assess the sphincter by SOM both the bile duct and pancreatic ducts must be evaluated. In a series [18] of 360 patients with pancreaticobiliary pain, 19% had abnormal pancreatic sphincter basal pressure alone, 11% had abnormal biliary basal sphincter pressure alone, and in 31%, the basal pressure was abnormal for both sphincters (overall frequency of SOD was 61%). Among the 214 patients labeled Type III, 17%, 11%, and 31% had elevated basal sphincter pressure in the pancreatic sphincter alone, biliary sphincter alone, or both the biliary and pancreatic sphincters respectively (overall frequency of SOD 59%). In the 123 patients labeled Type II, SOD was diagnosed in 65%; 22%, 11%, and 32% had the elevated basal sphincter pressure in the pancreatic sphincter only, biliary sphincter only, or both sphincters respectively.

Dysfunction may occur in the pancreatic duct portion of the SO and cause recurrent pancreatitis and pancreatic-type pain. Although a pancreatic SOD classification system has been developed (similar to the biliary SOD classification system), it has not been widely utilized [18]. Manometrically documented SOD has been reported in 15 to 72% of patients with recurrent pancreatitis, previously labeled as idiopathic [17, 18, 19].

**Clinical Presentation**

Abdominal pain is the most common presenting symptom of patients with SOD.
The pain is usually epigastric or right upper quadrant, may be disabling, and lasts for 30 minutes to several hours. In some patients the pain is continuous with episodic exacerbations. It may radiate to the back or shoulder and be accompanied by nausea and vomiting. Food or narcotics may precipitate the pain. The pain may begin several years after a cholecystectomy was performed for a gallbladder dysmotility or stone disease and is similar in character to the pain leading to the cholecystectomy. Alternatively, patients may have continued pain that was not relieved by a cholecystectomy. Jaundice, fever, or chills are rarely observed. The Rome II diagnostic criteria [7] for SOD are episodes of severe steady pain located in the epigastrium and right upper quadrant, and all of the following: 1) symptom episodes last 30 minutes or more with pain-free intervals; 2) symptoms have occurred on one or more occasions in the previous 12 months; 3) the pain is steady and interrupts daily activities or requires consultation with a physician; and 4) there is no evidence of structural abnormalities to explain the symptoms. Physical examination is characterized by the paucity of any abnormal findings. The most common physical finding is mild, nonspecific abdominal tenderness. The pain is not relieved by trial medications for acid-peptic disease or irritable bowel syndrome. Laboratory abnormalities consisting of transient elevation of liver function tests, typically during episodes of pain, are present in less than 50% of patients. After initial evaluation, patients are commonly categorized according to the Hogan-Geenen SOD classification system (Table 1). Patients with SOD may present with typical pancreatic pain (epigastric and/or left upper quadrant radiating to the back) and recurrent pancreatitis. SOD may exist in the presence of an intact biliary tract with the gallbladder in situ [20]. As the symptoms of SO or gallbladder dysfunction cannot be readily separated, the diagnosis of SOD is commonly made after cholecystectomy or less frequently after proper investigations have excluded gallbladder abnormalities [7].

Clinical Evaluation

The diagnostic approach to suspected SOD may be influenced by the presence of key clinical features. However, the clinical manifestations of functional abnormalities of the SO may not always be easily distinguishable from those caused by organic ones (e.g., common bile duct stones) or other functional non-pancreaticobiliary disorders (e.g., irritable bowel syndrome).

General Initial Evaluation

Evaluation of patients with suspected SOD (i.e., patients with upper abdominal pain with characteristics suggestive of a pancreatobiliary origin) should be initiated with standard serum liver chemistries, serum amylase and/or lipase, abdominal ultrasonography and/or computerized axial tomography (CAT) scans. The serum enzyme studies should be drawn during bouts of pain, if possible. Mild elevations (<2 x upper limits of normal) are frequent in SOD while greater abnormalities are more suggestive of stones, tumors, and liver parenchymal disease. Although the diagnostic sensitivity and specificity of abnormal serum liver chemistries are relatively low [21], recent evidence indicates that the finding of abnormal liver tests in biliary-Type II patients may predict a favorable response to endoscopic sphincterotomy [22]. CT scans and abdominal ultrasounds are usually normal but occasionally a dilated bile duct or pancreatic duct may be found (particularly in patients with Type I SOD). Standard evaluation and treatment of other more common upper gastrointestinal conditions, such as peptic ulcer disease and gastroesophageal reflux should be done simultaneously. In the absence of mass lesions, stones, or response to acid suppression therapeutic trials, the suspicion for sphincter disease is heightened.
Diagnostic Methods (Noninvasive)

Because SOM (considered by most authorities to be the gold standard for diagnosing SOD) is difficult to perform, invasive, not widely available, and associated with a relatively high complication rate, several noninvasive and provocative tests have been designed in an attempt to identify patients with SOD.

Morphine-Prostigmin Provocative Test (Nardi Test)

Morphine has been shown to cause sphincter of Oddi contraction. Prostigmin (Neostigmine), 1 mg. subcutaneously is added as a vigorous cholinergic secretory stimulant to morphine (10 mg subcutaneously) to make this challenge test. The morphine-prostigmin test, historically, had been used extensively to diagnose SOD. Reproduction of the patient's typical pain associated with a fourfold increase in AST, ALT, alkaline phosphatase, amylase, or lipase constitute a positive response. The usefulness of this test is limited by its low sensitivity and specificity in predicting the presence of SOD and its poor correlation with outcome after sphincter ablation [23]. This test has largely been replaced by tests believed to be more sensitive.

Ultrasonographic Assessment of Extrahepatic Bile Duct and Main Pancreatic Duct Diameter After Secretory Stimulation

After a lipid-rich meal or cholecystokinin administration, the gallbladder contracts, bile flow from the hepatocytes increases, and the sphincter of Oddi relaxes resulting in bile entry into the duodenum. Similarly, after a lipid-rich meal or secretin administration, pancreatic exocrine juice flow is stimulated and the sphincter of Oddi relaxes. If the sphincter of Oddi is dysfunctional and causes obstruction to flow, the common bile duct or main pancreatic duct may dilate under secretory pressure. This can be monitored by transcutaneous ultrasonography. Sphincter and terminal duct obstruction from other causes (stones, tumors, strictures, etc.) may similarly cause ductal dilation and need to be excluded. Pain provocation should also be noted if present. To date, limited studies comparing these noninvasive tests with sphincter of Oddi manometry or outcome after sphincter ablation show only modest correlation [24, 25, 26, 27, 28]. Because of intestinal gas, the pancreatic duct many not be visualized on standard transcutaneous ultrasound. Despite the superiority of endoscopic ultrasound in visualizing the pancreas, Catalano et al. [29] report the sensitivity of secretin-stimulated endoscopic ultrasound in detecting SOD to be only 57%.

Quantitative Hepatobiliary Scintigraphy

Hepatobiliary scintigraphy assesses bile flow through the biliary tract. Impairment to bile flow from sphincter disease, tumors, or stones (as well as parenchymal liver disease) results in impaired radionuclide flow. The precise criteria to define a positive (abnormal) study remain controversial, but duodenal arrival time greater than 20 minutes and hilum to duodenum time greater than 10 minutes are most widely used [30, 31, 32]. Most studies are flawed by lack of correlation with SOM or outcome after sphincter ablation. However, one study [33] did suggest that hepatobiliary scintigraphy significantly correlates with the sphincter of Oddi basal pressure. Overall, it appears that patients with dilated bile ducts and high-grade obstruction are likely to have a positive scintigraphic study. Esber and colleagues [34] found that patients with lower-grade obstruction (Hogan-Geenen classification Types II and III) generally have normal scintigraphy, even if done after cholecystokinin provocation.

The value of adding morphine provocation to hepatobiliary scintigraphy was recently reported [35]. Thirty-four patients with a clinical diagnosis of Type II and Type III SOD underwent hepatobiliary scintigraphy with and without morphine and subsequent biliary manometry. The standard hepatobiliary scan
did not distinguish between patients with normal and abnormal SOM. However, following provocation with morphine, there were significant differences in the time to maximal activity and the percentage of excretion at 45 and 60 minutes. Using a cut-off value of 15% excretion at 60 minutes, the sensitivity and specificity for detecting elevated SO basal pressures by morphine-augmented hepatobiliary scintigraphy were 83% and 81%, respectively.

In the absence of more definitive data, we currently conclude that noninvasive testing for sphincter of Oddi dysfunction has a relatively low or undefined sensitivity and specificity and is, therefore, not recommended for general clinical use, except in situations where more definitive testing (manometry) is unsuccessful or unavailable.

**Diagnostic Methods (Invasive)**

Because of their associated risks, invasive testing with ERCP and manometry should be reserved for patients with clinically significant or disabling symptoms. In general, invasive assessment of patients for SOD is not recommended unless definitive therapy (sphincter ablation) is planned if abnormal sphincter function is found.

**Cholangiography**

Cholangiography is essential to rule out stones, tumors, or other obstructing processes of the biliary tree that may cause symptoms identical to those of SOD. Once such lesions are ruled out by a good quality cholangiographic study, ducts which are dilated and/or drain slowly suggest obstruction at the level of the sphincter. A variety of methods to obtain a cholangiogram are available. Intravenous cholangiography has been replaced by more definitive methods. Helical-computed tomography cholangiography or magnetic resonance cholangiography appear promising but need further comparative analysis. Direct cholangiography can be obtained by percutaneous methods, intraoperative methods, or more conventionally at ERCP. Although some controversy exists, extrahepatic ducts that are greater than 12 mm in diameter (post cholecystectomy) when corrected for magnification, are considered dilated. Drainage of contrast is influenced by drugs which affect the rate of bile flow and relaxation or contraction of the sphincter of Oddi. Such drugs must be avoided to obtain accurate drainage times. Since the common bile duct angles from anterior to posterior, the patient must be supine to assess gravitational drainage through the sphincter. While definitive normal supine drainage times have not been well defined [36], a post cholecystectomy biliary tree that fails to empty all contrast media by 45 minutes is generally considered abnormal.

Endoscopic evaluation of the papilla and peripapillary area can yield important information that can influence the diagnosis and treatment of patients with suspected SOD. Occasionally, ampullary cancer may simulate SOD. The endoscopist should do tissue sampling of the papilla (preferably after sphincterotomy) in suspicious cases [37]. Radiographic features of the pancreatic duct are also important to assess in the patient with suspected SOD. Dilation of the pancreatic duct (≥ 6 mm in the pancreatic head and ≥ 5 mm in the body) and delayed contrast drainage time (≥ 9 min in the prone position) may give indirect evidence for the presence of SOD.

**Sphincter of Oddi Manometry**

The most definitive development in our understanding of the pressure dynamics of the SO came with the advent of SOM. SOM is the only available method to measure SO motor activity directly. Although SOM can be performed intraoperatively and percutaneously, it is most commonly done in the ERCP setting. SOM is considered by most authorities to be the gold standard for evaluating patients for sphincter dysfunction [38, 39]. The use of manometry to detect
motility disorders of the sphincter of Oddi is similar to its use in other parts of the gastrointestinal tract. Unlike other areas of the gut, SOM is more technically demanding and hazardous. Questions remain as to whether these short-term observations (2-10 minute recordings per pull-through) reflect the “24-hour pathophysiology” of the sphincter. Despite some problems, SOM is gaining more widespread clinical application.

**SOM Technique and Indications**

Sphincter of Oddi manometry is usually performed at the time of ERCP. All drugs which relax (anticholinergics, nitrates, calcium channel blockers, and glucagon) or stimulate (narcotics or cholinergic agents) the sphincter should be avoided for at least 8-12 hours prior to manometry and during the manometric session. The current data indicate that benzodiazepines do not affect the sphincter pressure and therefore are acceptable sedation for SOM. Recent data suggested that meperidine, at a dose of ≤1 mg/kg, does not affect the basal sphincter pressure (although it did affect the phasic wave characteristics) [40]. Since the basal sphincter pressure is generally the only manometric criterion used to diagnose sphincter of Oddi dysfunction and determine therapy, it was suggested that meperidine could be used to facilitate conscious sedation for SOM. Propofol is becoming increasingly utilized for SOM [41]. If glucagon must be used to achieve cannulation, an 8-10 minute (at least) waiting period is required to restore the sphincter to its basal condition.

Five-French catheters should be used, since virtually all standards have been established with these catheters. Triple-lumen catheters are state of the art and are available from several manufacturers. A variety of catheter types can be utilized. Catheters with a long intraductal tip may help secure the catheter within the bile duct, but such a long nose is commonly a hindrance if pancreatic manometry is desired. Over-the-wire (monorail) catheters can be passed after first securing one’s position within the duct with a guidewire. Some triple-lumen catheters will accommodate a 0.018-inch diameter guidewire passed through the entire length of the catheter and can be used to facilitate cannulation or maintain position in the duct. Guidewire-tipped catheters are being evaluated. Aspiration catheters in which one recording port is sacrificed to permit both end- and side-hole aspiration of intraductal juice and the perfusate are highly recommended for pancreatic manometry [42]. Most centers prefer to perfuse the catheters at 0.25 mL/channel using a minimally compliant pneumohydraulic capillary infusion system. Lower perfusion rates will give accurate basal sphincter pressures, but will not give accurate phasic wave information. The perfusate is generally distilled water, although physiologic saline needs further evaluation. The latter may crystallize in the capillary tubing of perfusion pumps and must be flushed out frequently.

Sphincter of Oddi manometry requires selective cannulation of the bile duct and/or pancreatic duct. The duct entered can be identified by gently aspirating on any port. The appearance of yellow-colored fluid in the endoscopic view indicates entry into the bile duct. Clear aspirate indicates that the pancreatic duct was entered. It is preferable to obtain a cholangiogram and/or pancreatogram prior to performing SOM as certain findings (e.g., common bile duct stone) may obviate the need for SOM. This can simply be done by injecting contrast through one of the perfusion ports. Blaut and colleagues [43] have recently shown that injection of contrast into the biliary tree prior to SOM does not significantly alter sphincter pressure characteristics. Similar evaluation of the pancreatic sphincter after contrast injection has not been reported. One must be certain that the manometry catheter is not impacted against the wall of the duct in order to assure accurate pressure measurements. Once deep cannulation is achieved and the patient acceptably sedated, the catheter is withdrawn across the sphincter at 1-2 mm intervals by standard station pull-through technique. Ideally, both the pancreatic and bile ducts should be studied. Current data indicate that an abnormal basal sphincter
pressure may be confined to one side of the sphincter in 35-65% of patients with abnormal manometry [18, 44, 45, 46, 47, 48]. Thus, one sphincter may be dysfunctional whereas the other normal. Raddawi and colleagues [44] reported that an abnormal basal sphincter was more likely to be confined to the pancreatic duct segment in patients with pancreatitis and to the bile duct segment in patients with biliary-type pain and elevated liver function tests.

Abnormalities of the basal sphincter pressure should ideally be observed for at least 30 seconds in each lead and be seen on two or more separate pull-throughs. From a practical clinical standpoint, we settle for one pull through (from each duct) if the readings are clearly normal or abnormal. During standard station pull-through technique, it is necessary to establish good communication between the endoscopist and the manometrist who is reading the tracing as it rolls off the recorder. This permits optimal positioning of the catheter in order to achieve interpretable tracings. Once the baseline study is done, agents to relax or stimulate the sphincter can be given (example: cholecystokinin) and manometric and/or pain response monitored. The value of these provocative maneuvers for everyday use needs further study before widespread application is recommended.

Criteria for interpretation of a SO tracing are relatively standard; however, they may vary somewhat from center to center. Some areas where there may be disagreement in interpretation include the required duration of basal SO pressure elevation, the number of leads in which basal pressure elevation is required, and the role of averaging pressures from the three (or two in an aspirating catheter) recording ports [2]. Our recommended method for reading the manometry tracings is to first define the “zero” duodenal baseline before and after the pull-through. Alternatively, intraduodenal pressure can be continuously recorded from a separate intraduodenal catheter attached to the endoscope. Identify the highest basal pressure (Figure 1) that is sustained for at least 30 seconds (and preferably over one minute). Take the four lowest amplitude points in that zone and take the mean of these readings as the basal sphincter pressure for that lead for that pull-through. Average the basal sphincter pressure for all interpretable observations and take this as the final basal sphincter pressure. The amplitude of phasic wave contractions is measured from the beginning of the slope of the pressure increase from the basal pressure to the peak of the contraction wave. Four representative waves are taken for each lead and the mean pressure determined. The number of phasic waves per minute and the duration of the phasic waves can also be determined. Most authorities read only the basal sphincter pressure as an indicator of pathology of the SO. However, data from Kalloo and colleagues [49] suggest that intrabiliary pressure (which is easier to measure than SO pressure) correlates with SO basal pressure. In this study, intrabiliary pressure was significantly higher in patients with SOD than those with normal SO pressure (20 vs. 10 mmHg; P<0.01). This study needs to be confirmed but supports the theory that increased intrabiliary pressure is a cause of pain in SOD.

The best study establishing normal values for sphincter of Oddi manometry was reported by Guelrud and associates [50]. Fifty asymptomatic control patients were evaluated and the study was repeated on two occasions in 10 subjects. This study established normal values for intraductal pressure, basal sphincter pressure, and phasic wave parameters (Table

![Schematic representation of a sphincter of Oddi manometry recording. Note that the basal sphincter pressure is the baseline pressure between phasic waves (using the duodenal pressure as the zero reference point). (CBD: common bile duct; SO: sphincter of Oddi).](image-url)
Moreover, the reproducibility of SOM was confirmed. Various authorities interchangeably use 35 mmHg or 40 mmHg as the upper limits of normal for mean basal sphincter of Oddi pressure.

Several studies have indicated that pancreatitis is the most common major complication after SOM [42, 51, 52]. Using standard perfused catheters, pancreatitis rates as high as 31% have been reported. Such high complication rates have initially limited more widespread use of SOM. These data also emphasize that manometric evaluation of the pancreatic duct, particularly in patients with chronic pancreatitis, is associated with a high complication rate. Rolny and associates reported an 11% incidence of pancreatitis following pancreatic duct manometry [51]. Twenty-six percent of chronic pancreatitis patients undergoing SOM developed pancreatitis. A variety of methods to decrease the incidence of post-manometry pancreatitis have been proposed. These include: 1) use of an aspiration catheter; 2) gravity drainage of the pancreatic duct after manometry; 3) decrease the perfusion rate to 0.05-0.1 mL/lumen/minute; 4) limit pancreatic duct manometry time to less than 2 minutes (or avoid pancreatic manometry); 5) use the microtransducer (non-perfused) system [17]. In a prospective randomized study, Sherman and colleagues found that the aspirating catheter (this catheter allows for aspiration of the perfused fluid from end and side holes while accurately recording pressure from the two remaining sideports) reduced the frequency of pancreatic duct manometry-induced pancreatitis from 31 to 4% [42]. The reduction in pancreatitis with use of this catheter in the pancreatic duct and the very low incidence of pancreatitis after bile duct manometry lend support to the notion that increased pancreatic duct hydrostatic pressure is a major cause of this complication. Thus, when we study the pancreatic duct sphincter by SOM, we routinely aspirate pancreatic juice. SOM is recommended in patients with idiopathic pancreatitis or unexplained disabling pancreaticobiliary pain with or without hepatic enzyme abnormalities. An attempt is made to study both sphincters, but clinical decisions can be made when the first sphincter evaluated is abnormal. An ERCP is usually performed (if an adequate study is not available) immediately before the SOM to exclude other potential causes for the patient's symptoms. Indications for the use of SOM have also been developed according to the Hogan-Geenen SOD classification system (Table 1). In Type I patients, there is a general consensus that a structural disorder of the sphincter (i.e., sphincter stenosis) exists. Although SOM may be useful in documenting SOD, it is not an essential diagnostic study prior to endoscopic or surgical sphincter ablation. Such patients uniformly benefit from sphincter ablation regardless of the SOM results (see below). Type II patients demonstrate SO motor dysfunction in 50 to 65% of cases. In this group of patients, SOM is highly recommended as the results of the study predict outcome from sphincter ablation. Type III patients have pancreaticobiliary pain without other objective evidence of sphincter outflow obstruction. SOM is mandatory to confirm the presence of SOD. Although not well studied, it appears that the results of SOM may predict outcome from sphincter ablation in these patients.

Table 2. Suggested standard for abnormal values for endoscopic sphincter of Oddi manometry obtained from 50 volunteers without abdominal symptoms.

<table>
<thead>
<tr>
<th>Basal sphincter pressure*</th>
<th>&gt;35 mmHg</th>
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<tr>
<td>Basal ductal pressure</td>
<td>&gt;13 mmHg</td>
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<td>Phasic contractions</td>
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<td>- Amplitude</td>
<td>&gt;220 mmHg</td>
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<td>- Duration</td>
<td>&gt;8 sec</td>
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<tr>
<td>- Frequency</td>
<td>&gt;10/min</td>
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Note: Values were obtained by adding 3 standard deviations to the mean (means were obtained by averaging the results on 2-3 station pull-throughs). Data combine pancreatic and biliary studies.

* Basal pressures determined by: 1) reading the peak basal pressure (i.e., highest single lead as obtained using a 3 lumen catheter); 2) obtaining the mean of these peak pressures from multiple station pull-throughs.

Adapted from reference [50]
**Stent Trial as Diagnostic Test**

Placement of a pancreatic or biliary stent on a trial basis in hope of achieving pain relief and predicting the response to more definitive therapy, i.e., sphincter ablation, has received only limited application. Pancreatic stent trials, especially in patients with normal pancreatic ducts, are strongly discouraged as serious ductal and parenchymal injury may occur if stents are left in place for more than a few days [53]. Goff reported a biliary stent trial in 21 Type II and III SOD patients with normal biliary manometry [54]. Seven-French stents were left in place for at least 2 months if symptoms resolved and removed sooner if they were judged ineffective. Relief of pain with the stent was predictive of long term pain relief after biliary sphincterotomy. Unfortunately, 38% of the patients developed pancreatitis (14% were graded severe) following stent placement. Because of this high rate of complications, biliary stent trials are strongly discouraged. Rolny and colleagues also reported a series of bile duct stent placement as predictor of outcome following endoscopic sphincterotomy in 23 post-cholecystectomy patients (7 Type II and 16 Type III) [55]. Similar to the study by Goff [54], resolution of pain during at least 12 weeks of stenting predicted a favorable outcome from sphincterotomy irrespective of sphincter of Oddi pressure. In this series there were no complications related to stent placement.

**Therapy for SOD**

The therapeutic approach in patients with SOD is aimed at reducing the resistance caused by the sphincter of Oddi to the flow of bile and/or pancreatic juice [7]. The therapy of SOD is evolving. Historically, most emphasis has been placed on definitive intervention, i.e., surgical sphincteroplasty or endoscopic sphincterotomy. This appears appropriate for patients with high-grade obstruction (Type I as per Hogan-Geenen criteria). In patients with lesser degrees of obstruction, the clinician must carefully weigh the risks and benefits before recommending invasive therapy. Most reports indicate that SOD patients have a complication rate from endoscopic sphincterotomy of at least twice that of patients with ductal stones.

**Medical Therapy**

Medical therapy for documented or suspected SOD has received only limited study. Because the SO is a smooth muscle structure, it is reasonable to assume that drugs that relax smooth muscle might be an effective treatment for SOD. Sublingual nifedipine and nitrates have been shown to reduce the basal sphincter pressures in asymptomatic volunteers and symptomatic patients with SOD [1, 56]. Khuroo and colleagues [57] evaluated the clinical benefit of nifedipine in a placebo controlled crossover trial. Twenty-one of 28 patients (75%) with manometrically documented SOD had a reduction in pain scores, emergency room visits and use of oral analgesics during short-term follow-up. In a similar study, Sand et al. [58] found that 9 of 12 (75%) Type II SOD (suspected; SOM was not done) patients improved with nifedipine. Although medical therapy may be an attractive initial approach in patients with SOD, several drawbacks exist [1]. First, medication side-effects may be seen in up to one-third of patients. Second, smooth muscle relaxants are unlikely to be of any benefit in patients with the structural form of SOD (i.e., SO stenosis) and the response is incomplete in patients with a primary motor abnormality of the SO (i.e., SO dyskinesia). Finally, long-term outcome from medical therapy has not been reported. Nevertheless, because of the “relative safety” of medical therapy and the benign (though painful) character of SOD, this approach should be considered in all Type III and less severely symptomatic Type II SOD patients before considering more aggressive sphincter ablation therapy. Guelrud and colleagues have demonstrated [59] that transcutaneous electrical nerve stimulation (TENS) lowers the basal sphincter
pressure in SOD patients by a mean of 38% (but unfortunately, generally not into the normal range). This stimulation was associated with an increase in serum VIP levels. Electroacupuncture applied at acupoint GB 34 (a specific acupoint that affects the hepatobiliary system) was shown to relax the sphincter of Oddi in association with increased plasma CCK levels [60]. Its role in the management of SOD has not been investigated.

**Surgical Therapy**

Surgery was the traditional therapy of SOD. The surgical approach, most commonly, is a transduodenal biliary sphincteroplasty with a transampullary septoplasty (pancreatic septoplasty). Sixty to seventy percent of patients were reported to have benefited from this therapy during a 1-10 year follow-up [61, 62]. Patients with an elevated basal sphincter pressure determined by intraoperative SOM were more likely to improve from surgical sphincter ablation than those with a normal basal pressure [62]. Some reports have suggested that patients with biliary-type pain have a better outcome than patients with idiopathic pancreatitis while others suggested no difference [61, 62]. However, most studies found that symptom improvement following surgical sphincter ablation alone was relatively uncommon in patients with established chronic pancreatitis [62]. The surgical approach for SOD has largely been replaced by endoscopic therapy. Patient tolerance, cost of care, morbidity, mortality, and cosmetic results are some of the factors that favor an initial endoscopic approach. At present, surgical therapy is reserved for patients with restenosis following endoscopic sphincterotomy and when endoscopic evaluation and/or therapy is not available or technically feasible. In many centers, however, operative therapy continues to be the standard treatment of pancreatic sphincter hypertension [7, 63].

**Endoscopy Therapy**

Endoscopic sphincterotomy. Endoscopic sphincterotomy is the current standard therapy for patients with SOD. Most data on endoscopic sphincterotomy relates to biliary sphincter ablation alone. Clinical improvement following therapy has been reported to occur in 55-95% of patients (Table 1). These variable outcomes are reflective of the different criteria used to document SOD, the degree of obstruction (Type I biliary patients appear to have a better outcome than Type II and III), the methods of data collection (retrospective vs. prospective), and the techniques used to determine benefit. Rolny and colleagues [64] studied 17 Type I post-cholecystectomy biliary patients by SOM. In this series, 65% had an abnormal SOM (although not specifically stated, it appears that the biliary sphincter was studied alone). Nevertheless, during a mean follow-up interval of 2.3 years, all patients benefited from biliary sphincterotomy. The results of this study suggested that since Type I biliary patients invariably benefit from biliary sphincterotomy, SOM in this patient group is not only unnecessary, but it may also be misleading. The results of this study, however, have never been validated at another center. Although most of the studies reporting efficacy of endoscopic therapy in SOD have been retrospective, three notable randomized trials have now been reported. In a landmark study by Geenen and associates [65], 47 post-cholecystectomy Type II biliary patients were randomized to biliary sphincterotomy or sham sphincterotomy. SOM was performed in all patients but not used as a criterion for randomization. During a 4-year follow-up, 95% of patients with an elevated basal sphincter benefited from sphincterotomy. In contrast, only 30-40% of patients with an elevated sphincter pressure treated by sham sphincterotomy or with a normal sphincter pressure treated by endoscopic...
sphincterotomy or sham sphincterotomy benefited from this therapy. The two important findings of this study were that SOM predicted the outcome from endoscopic sphincterotomy and that endoscopic sphincterotomy offered long-term benefit in Type II biliary patients with SOD.

Sherman and associates [66] reported their preliminary results of a randomized study comparing endoscopic sphincterotomy, surgical biliary sphincteroplasty with pancreatic septoplasty (with or without cholecystectomy) to sham sphincterotomy for Type II and III biliary patients with manometrically documented SOD. The results are shown on Tables 3a and 3b. During a 3.0 year follow-up period, 69% of patients undergoing endoscopic or surgical sphincter ablation improved compared to 24% in the sham sphincterotomy group (P=0.009). There was a trend for Type II patients to benefit more frequently from sphincter ablation than Type III (13/16, 81% vs. 11/19, 58%; P=0.14). Evidence is now accumulating that the addition of a pancreatic sphincterotomy to an endoscopic biliary sphincterotomy in such patients may improve the outcome (see below). Long-term outcome studies, preferably in randomized trials, are awaited.

In a third study [67, 68], post-cholecystectomy patients with biliary-type pain (mostly Type II) were prospectively randomized to endoscopic sphincterotomy or sham following stratification according to SOM. Eighty-five percent (11 of 13) of patients with elevated basal pressure improved at 2 years after endoscopic sphincterotomy, while 38% (5 of 13) of patients improved after a sham procedure (P=0.041). Patients with normal SOM were also randomized to sphincterotomy or sham. The outcome was similar for the two groups (8 of 13 improved after sphincterotomy and 8 of 19 improved after sham; P=0.47).

These results clearly indicate that the response rate and enthusiasm for sphincter ablation must be correlated with patient presentation and balanced against the high complication rates reported for endoscopic therapy of SOD. Most studies indicate that patients undergoing endoscopic sphincterotomy for SOD have complication rates 2-5 times higher than patients undergoing endoscopic sphincterotomy for ductal stones [69, 70]. Pancreatitis is the most common complication occurring in up to 20% of patients. Endoscopic techniques are being developed (e.g., pancreatic duct stenting prior to combined pancreaticobiliary sphincterotomy and pancreatic stenting after biliary sphincterotomy) to limit such complications [71].

Balloon dilation and stenting. Balloon dilation of strictures in the gastrointestinal tract has become commonplace. In an attempt to be less

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**Table 3a.** Change in the mean pain score (using a 0-none to 10-most severe linear pain scale) and number of hospital days per month required for pain in patients with manometrically documented sphincter of Oddi dysfunction randomized to endoscopic sphincterotomy (ES), sham sphincterotomy (S-ES), and surgical sphincteroplasty with or without cholecystectomy (SSp±CCx).

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Follow-up (yrs)</th>
<th>Mean pain score</th>
<th>Hospital days/month</th>
<th>% patients improved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-Rx</td>
<td>Post-Rx</td>
<td>Pre-Rx</td>
</tr>
<tr>
<td>ES (n=19)</td>
<td>3.3</td>
<td>9.2</td>
<td>3.9a</td>
<td>0.85</td>
</tr>
<tr>
<td>S-ES (n=17)</td>
<td>2.2</td>
<td>9.4</td>
<td>7.2</td>
<td>0.87</td>
</tr>
<tr>
<td>SSp±CCx (n=16)</td>
<td>3.4</td>
<td>9.4</td>
<td>3.3c</td>
<td>0.94</td>
</tr>
</tbody>
</table>

*a P<0.04; a P=0.002; c P=0.009; ES and SSp±CCx vs. S-ES Adapted from reference [66]

**Table 3b.** Clinical benefit correlated with sphincter of Oddi dysfunction (SOD) type.

<table>
<thead>
<tr>
<th>SOD Type*</th>
<th>Patients improved / total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ES</td>
</tr>
<tr>
<td>Type II</td>
<td>5/6 (83%)a</td>
</tr>
<tr>
<td>Type III</td>
<td>8/13 (62%)a</td>
</tr>
</tbody>
</table>

*a P<0.02; ES and SSp±CCx vs. S-ES Adapted from reference [66]
invasive and possibly preserve sphincter function, adaptation of this technique to treat SOD has been described. Unfortunately because of the unacceptably high complication rates, primarily pancreatitis, this technology has little role in the management of SOD [72]. Similarly, although biliary stenting might offer short-term symptom benefit in patients with SOD and predict outcome from sphincter ablation, it too has unacceptably high complication rates and cannot be advocated in this setting based on the available data [54].

Botulinum toxin injection. Botulinum toxin (Botox), a potent inhibitor of acetylcholine release from nerve endings, has been successfully applied to smooth muscle disorders of the gastrointestinal tract such as achalasia. In a preliminary clinical trial, Botox injection into the SO resulted in a 50% reduction in the basal sphincter pressure and improved bile flow [73]. This reduction in pressure may be accompanied by symptom improvement in some patients. Although further study is warranted, Botox may serve as a therapeutic trial for SOD with responders undergoing permanent sphincter ablation. One such study has recently been reported [74]. Twenty-two post-cholecystectomy Type III patients with manometric evidence of SOD underwent Botox injection into the intraduodenal sphincter segment. Overall, 11 of the 12 patients who responded to botulinum toxin versus 2 of 10 patients who did not gain pain relief, later benefited from endoscopic sphincterotomy (P<0.01).

**SOD in Recurrent Pancreatitis**

Disorders of the pancreatic sphincter can give rise to pancreatitis or episodic pain suggesting a pancreatic origin [63]. SOD has been manometrically documented in 15 to 72% of patients with recurrent pancreatitis, previously labeled as idiopathic [17, 18, 19, 75]. Biliary sphincterotomy alone has been reported to prevent further pancreatitis episodes in more than 50% of such patients. From a scientific, but not practical viewpoint, care must be taken to separate out subtle biliary pancreatitis [76] which will similarly respond to biliary sphincterotomy.

The value of ERCP, SOM and sphincter ablation therapy was studied in 51 patients with idiopathic pancreatitis [39]. Twenty-four (47.1%) had an elevated basal sphincter pressure. Thirty were treated by biliary sphincterotomy (n=20), or surgical sphincteroplasty with pancreatic septoplasty (n=10). Fifteen of 18 patients (83%) with an elevated basal sphincter pressure had long-term benefit (mean follow-up, 38 months) from sphincter ablation therapy (including 10 of 11 treated by biliary sphincterotomy) in contrast to only 4 of 12 (33.3%, P<0.05) with a normal basal sphincter pressure (including 4 of 9 treated by biliary sphincterotomy). However, Guelrud *et al.* [77] found that severance of the pancreatic sphincter was necessary to resolve the pancreatitis (Table 4).

In this series, 69 patients with idiopathic pancreatitis due to SOD underwent treatment by standard biliary sphincterotomy (n=18), biliary sphincterotomy with pancreatic sphincter balloon dilation (n=24), biliary sphincterotomy followed by pancreatic sphincterotomy in separate sessions (n=13), or combined pancreatic and biliary sphincterotomy in the same session (n=14).

<table>
<thead>
<tr>
<th>Table 4. Pancreatic sphincter dysfunction and recurrent pancreatitis: response to sphincter therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>Biliary sphincterotomy alone</td>
</tr>
<tr>
<td>Biliary sphincterotomy followed by pancreatic sphincter balloon dilation</td>
</tr>
<tr>
<td>Biliary sphincterotomy plus pancreatic sphincterotomy at later session</td>
</tr>
<tr>
<td>Biliary sphincterotomy and pancreatic sphincterotomy at same session</td>
</tr>
</tbody>
</table>

^a P<0.005 vs. biliary sphincterotomy alone

Adapted from reference [77]
Eighty-one percent of patients undergoing pancreatic and biliary sphincterotomy had resolution of their pancreatitis compared to 28% of patients undergoing biliary sphincterotomy alone (P<0.005). These data are consistent with the theory that many such patients who benefit from biliary sphincterotomy alone have subtle gallstone pancreatitis. The results of Guelrud et al. [77] also support the anatomic findings of separate biliary and pancreatic sphincters, and the manometry findings of residual pancreatic sphincter hypertension in more than 50% of persistently symptomatic patients who undergo biliary sphincterotomy alone. Toouli et al. [78] also demonstrated the importance of pancreatic and biliary sphincter ablation in patients with idiopathic pancreatitis. In this series, 23 of 26 patients (88%) undergoing surgical ablation of both the biliary and pancreatic sphincter were either asymptomatic or had minimal symptoms at a median follow-up of 24 months (range, 9-105 months). Okolo and colleagues [79] retrospectively evaluated the long-term results of endoscopic pancreatic sphincterotomy in 55 patients with presumed (recurrent pancreatitis with pancreatic duct dilation and contrast medium drainage time from the pancreatic duct greater than 10 minutes) or manometrically documented pancreatic sphincter dysfunction. During a median follow-up of 16 months (range, 3-52 months), 34 patients (62%) reported significant pain improvement. Patients with normal pancreatograms were more likely to respond to therapy than were those with pancreatographic evidence of chronic pancreatitis (73% vs. 58%).

Currently, the best method to treat residual pancreatic sphincter stenosis after biliary sphincterotomy awaits further study. Patients with idiopathic pancreatitis who fail to respond to biliary sphincterotomy alone should have their pancreatic sphincter reevaluated and be considered for sphincter ablation if residual high pressure is found.

### Table 5. Causes for failure to achieve symptom relief after biliary sphincterotomy in sphincter of Oddi dysfunction.

1. Residual or recurrent biliary sphincter dysfunction
2. Pancreatic sphincter (major papilla) dysfunction
3. Chronic pancreatitis - subtle, pancreatogram normal
4. Other obstructive pancreatobiliary pathology (stones, strictures, tumor, pancreas divisum)
5. Non-pancreatobiliary disease - especially gut motor disorders or irritable bowel syndrome

Failure to Achieve Symptomatic Improvement after Biliary Sphincterectomy

Table 5 lists several potential explanations as to why patients may fail to achieve symptom relief after biliary sphincterotomy is performed for well-documented sphincter of Oddi dysfunction. First, the biliary sphincterotomy may have been inadequate or restenosis may have occurred. Although the biliary sphincter is commonly not totally ablated [80], Manoukian et al. indicate that clinically significant biliary restenosis occurs relatively infrequently [81]. If no "cutting space" remains in such a patient, balloon dilation to 8-10 mm may suffice, but long-term outcome from such therapy is unknown [72].

Second, the importance of pancreatic sphincter ablation is being increasingly recognized, as noted in the data preliminarily reported by Guelrud et al. [77]. Eversman and colleagues found that 90% of patients with persistent pain or pancreatitis after biliary sphincterotomy had residual abnormal pancreatic basal pressure [82]. Soffer and Johlin reported that 25 of 26 patients (mostly Type II), who failed to respond to biliary sphincterotomy, had elevated pancreatic sphincter pressure [83]. Endoscopic pancreatic sphincterotomy was performed with overall symptomatic improvement in two thirds of patients. Elton and colleagues [84] performed pancreatic sphincterotomy on 43
Type I and Type II SOD patients who failed to benefit from biliary sphincterotomy alone. During the follow-up period, 72% were symptom-free and 19% were partially or transiently improved.

Third, patients may fail to respond to sphincterotomy because they have chronic pancreatitis. These people may or may not have abnormal pancreatograms. Intraductal pancreatic juice aspiration after secretin stimulation may help make this diagnosis [85, 86]. Endoscopic ultrasound may show parenchymal and ductular changes of the pancreas in some of these patients suggesting chronic pancreatitis [87].

Fourth, some patients may be having pain from altered gut motility of the stomach, small bowel or colon (irritable bowel or pseudo-obstruction variants). There is increasing evidence that upper GI motility disorders may masquerade as pancreatobiliary-type pain (i.e., discrete right upper quadrant pain). Multiple preliminary studies show disordered duodenal motility in such patients [88, 89, 90]. This area needs much more study to determine the frequency, significance, and/or coexistence of these motor disorders along with SOD. A recent study [91] suggested that Type III patients have duodenal specific visceral hyperalgesia with pain reproduction by duodenal distention. These patients were also shown to have high levels of somatization, depression, obsessive-compulsive behavior, and anxiety compared to control subject [92].

Summary

In summary, our knowledge of sphincter of Oddi dysfunction and manometric techniques to assist in this diagnosis are evolving. Successful endoscopic SOM requires good general ERCP skills and careful attention to the main details listed above. If SOD is suspected in a Type III or mild to moderate pain level Type II patient, medical therapy should generally be tried. If medical therapy fails or is bypassed, ERCP and manometric evaluation are recommended. The role of less-invasive studies remains uncertain due to undefined sensitivity and specificity. Sphincter ablation is generally warranted in symptomatic Type I patients and Type II and III patients with abnormal manometry. The symptom relief rate varies from 55 to 95%, depending on the patient presentation and selection. Initial non-responders require thorough pancreatic sphincter and pancreatic parenchymal evaluation. SOD patients have relatively high complication rates after invasive studies or therapy. Thorough review of the risk: benefit ratio with individual patients is mandatory.

Key words Cholangiopancreatography, Endoscopic Retrograde; Manometry; Oddi's Sphincter; Pancreatitis, Acute Necrotizing; Sphincterotomy, Endoscopic

Abbreviations CAT: computerized axial tomography; MMC: migrating motor complex; SO: sphincter of Oddi; SOD: sphincter of Oddi dysfunction; SOM: SO manometry; TENS: transcutaneous electrical nerve stimulation; VIP: vasoactive intestinal peptide

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