Gastroenterology 2026;170:1303–1317

Gallbladder and Sphincter of Oddi Disorders

B. Joseph Elmunzer,[1] Emily Winslow,[2] Roberto De Giorgio,[3] Andrea Laghi,[4] Marianna Arvanitakis,[5] Grace Elta,[6] and Enrico Corazziari[7]

[1]Division of Gastroenterology and Center for Digestive Health and Surgery, Atrium Health-Wake Forest University School of Medicine, Charlotte, North Carolina; [2]Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; [3]Department of Translational Medicine, University of Ferrara, Ferrara, Italy; [4]Department of Biomedical Sciences, Humanitas University, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [5]Department of Gastroenterology, Hepatopancreatology, and Digestive Oncology, Hôpital Universitaire de Bruxelles Erasme Hospital and Research Unit in Cardiorespiratory Physiology and Exercise Nutrition, Faculty of Human Movement Sciences, Université libre de Bruxelles, Brussels, Belgium; [6]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan; and [7]Department of Gastroenterology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

Dysfunctional gallbladder disorder (DGBD) and sphincter of Oddi disorder (SOD) are possible causes of abdominal pain, biliary obstruction, and acute pancreatitis, and are often invoked when a structural etiology is not obvious. Diagnosis was traditionally based on gallbladder scintigraphy and sphincter of Oddi manometry, both of which have fallen out of favor and are no longer part of the Rome Diagnostic Criteria. For DGBD, the presence of typical biliary pain and persistence of symptoms despite watchful waiting, and for SOD, objective evidence of biliary obstruction and pancreatitis are now central to the diagnosis. With growing recognition that these disorders have traditionally been overdiagnosed and their treatments, which are risky, have been overused, the approach to cholecystectomy and endoscopic retrograde cholangiopancreatography has become progressively more restrictive. This trend continues in Rome V, although predictors of response to therapy, especially for biliary and pancreatic SOD, are desperately needed.

Keywords: Dysfunctional Gallbladder Disorder; Sphincter of Oddi Disorder; Sphincter of Oddi Dysfunction; Idiopathic Recurrent Acute Pancreatitis.

Dysfunction of the gallbladder (GB) and sphincter of Oddi (SO)—often invoked in the pathogenesis of unexplained upper abdominal pain, biliary obstruction, and recurrent acute pancreatitis (RAP)—first appeared in Rome I but remains understudied. GB and SO disorders are not typically perceived to be classic disorders of gut–brain interaction (DGBI) because the pathophysiological defect is generally believed to occur at the level of the GB or pancreaticobiliary sphincter complex, and the putative cure is elimination of the responsible anatomic structure. However, it remains unclear how much of the disease process is truly attributable to the GB or SO as opposed to the enteric nervous system. Regardless of where these disorders fall on the spectrum of neuroenteric dysregulation, they are at the very least strongly interconnected with DGBI, given their potentially intertwined pathophysiology and highly overlapping symptomatology.

With growing understanding, it has become clear that most patients traditionally diagnosed with GB or SO dysfunction have instead experienced a more classic DGBI. On this basis, and considering the significant risks of intervention, treatment for GB and SO disorders has become progressively more restrictive, ideally reserved for those who are most likely to benefit, although reliable predictors of response remain elusive. Although progress has been slow, some important advances in the evaluation and treatment of these disorders have been made since Rome IV and are highlighted in this review, with an emphasis on minimizing harm and optimizing the risk to benefit ratio of intervention.

Typical Biliary Pain

Abdominal pain is the cardinal symptom of GB and SO dysfunction, and the interpretation of pain is central to the diagnostic approach. A principal challenge in the evaluation of patients with a suspected GB or SO disorder is difficulty in characterization of biliary pain, which can be nonspecific in terms of both its location and qualitative attributes. Common misconceptions are that the pain syndrome is colicky and that it is restricted to the right upper quadrant. However, unlike the fluctuating pain of renal colic or intestinal obstruction, biliary pain typically reaches its maximal intensity quickly and then remains steady (Figure 1). In addition, experimental data and clinical observation suggest biliary pain most commonly involves the epigastrium.[1] To further confuse matters, because of diffuse innervation, experimental distention of other

Abbreviations used in this paper: **CS, cholescintigraphy; DGBD, dysfunctional gallbladder disorder; DGBI, disorders of gut–brain interaction; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; GB, gallbladder; GBEF, gallbladder ejection fraction; MRCP, magnetic resonance cholangiopancreatography; RAP, recurrent acute pancreatitis; SO, sphincter of Oddi; SOD, sphincter of Oddi disorder.**

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2026.01.035

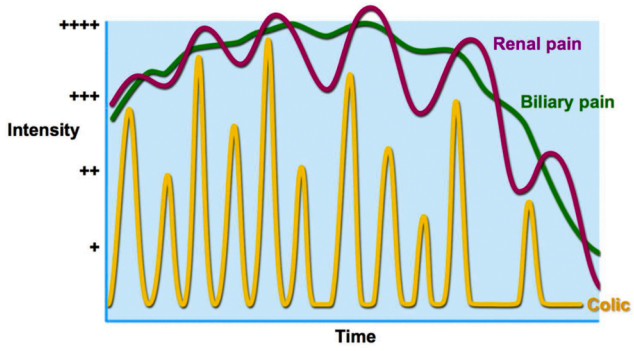

Figure 1. The sustained pattern of typical biliary pain relative to the more undulating pattern of renal pain and the intermittent nature of true intestinal colic.

organs, including the esophagus, duodenum, ileum, and colon, can reproduce the same kind of pain.[2,3]

The Rome V definition of typical biliary pain is listed in Box 1. Compared with Rome IV, the term "criteria" was replaced with "definition" because pain is a symptom, not a diagnosis, and the term "typical" was added to denote that the pain syndrome that is most likely to manifest in patients with true GB or SO dysfunction (ie, those who respond to therapy) mimics the pain that patients typically feel when experiencing transient obstruction of the cystic duct or bile duct by a gallstone. It is important to recognize, however, that there are relatively limited data to support this contention, especially for sphincter disorders. Moreover, it is reasonable to expect that some patients with static abnormalities of the GB or SO (such as those with chronic cholecystitis, which is observed in some patients who have GB dyskinesia or those with high-grade biliary obstruction due to SO stenosis) might experience a more continuous pain pattern. Nevertheless, given the risks of cholecystectomy and especially endoscopic retrograde cholangiopancreatography (ERCP) in this patient population, and the remaining uncertainties around efficacy, it is important to use a more thoughtful and restrictive approach to therapy. One such approach to patient selection is the use of a more stringent definition of biliary pain, recognizing that there will be exceptions to this definition depending on clinical context.

Box 1. Definition of Typical Biliary Pain

Pain located in the epigastrium and/or right upper quadrant, and *all* of the following:
1. Acute onset, lasting at least 20 minutes and up to several hours
2. Episodic, with varying intervals between attacks
3. Severe enough to interrupt daily activities or lead to acute medical evaluation
4. Unrelated to bowel movements and not relieved by acid suppression or positional changes

Supportive characteristics:
1. Nausea and vomiting
2. Pain radiates to the back and/or right shoulder blade
3. Pain occurs postprandially
4. Pain awakens patient from sleep

Dysfunctional Gallbladder Disorder

Definition

The concept that an acalculous GB can cause biliary pain that is cured by cholecystectomy has been assigned a variety of terms, including GB dyskinesia, biliary dyskinesia, chronic acalculous GB dysfunction, and chronic acalculous cholecystitis. However, these terms aim to suggest the pathogenesis or pathophysiology of the disorder, which is not always demonstrable. Not all GBs resected for the suspicion of causing biliary pain have motor abnormalities, and the motor dysfunction seen in many diseases, such as gallstones, obesity, and diabetes, does not always cause pain. To mitigate the uncertainties around terminology that invokes a pathologic or pathophysiologic process and in accordance with Rome consensus nomenclature, we use the term "dysfunctional gallbladder disorder" (DGBD) to indicate biliary-type pain believed to originate from GB dysfunction.

Epidemiology

Our understanding of the epidemiology of DGBD is based on surgical series that may exaggerate prevalence due to referral bias and overutilization of cholecystectomy for this indication, likely mirroring the widespread diffusion of minimally invasive approaches to the operation. Large case series have listed biliary dyskinesia as the primary reason for cholecystectomy in up to approximately 40% of adults[4] and approximately 60% of children.[5] A longitudinal examination of the Nationwide Inpatient Sample highlighted the rapid increase in cholecystectomy for suspected DGBD over the 20-year period between 1991 and 2011, from 43 to 89 per 1,000,000 population, much higher than that observed in international cohorts (typically $<$25 per 1,000,000 population).[6]

However, the true prevalence of DGBD itself is unknown. A large Italian cohort study of civil servants in the mid-1980s reported that 7.6% of men and 20.7% of women experienced biliary pain without any ultrasonographic evidence of gallstones.[7] In contrast, using the Rome IV definition of functional biliary pain, the Rome Global Epidemiology Study found an overall prevalence of $<$1%, with only a fraction of this representing DGBD.[8] This low prevalence may reflect the strict nature of the definition; however, the sizeable discrepancy between the number of people who meet the definition and those undergoing cholecystectomy for suspected DGBD suggests overutilization of the operation.

Pathophysiology and Psychological Features

The presumed pathophysiological factors that are relevant in the development of DGBD are depicted in Figure 2 and relate to the following 3 components of the GB itself: (1) bile within its lumen, (2) the GB epithelium, and (3) the GB wall musculature. Each factor can become disordered enough to induce reciprocal deleterious interactions with the other factors through altered crosstalk, worsening the initial state. The end result of this disordered triumvirate is GB inflammation and dysmotility, which are likely to exacerbate one another, resulting in a vicious cycle. An important

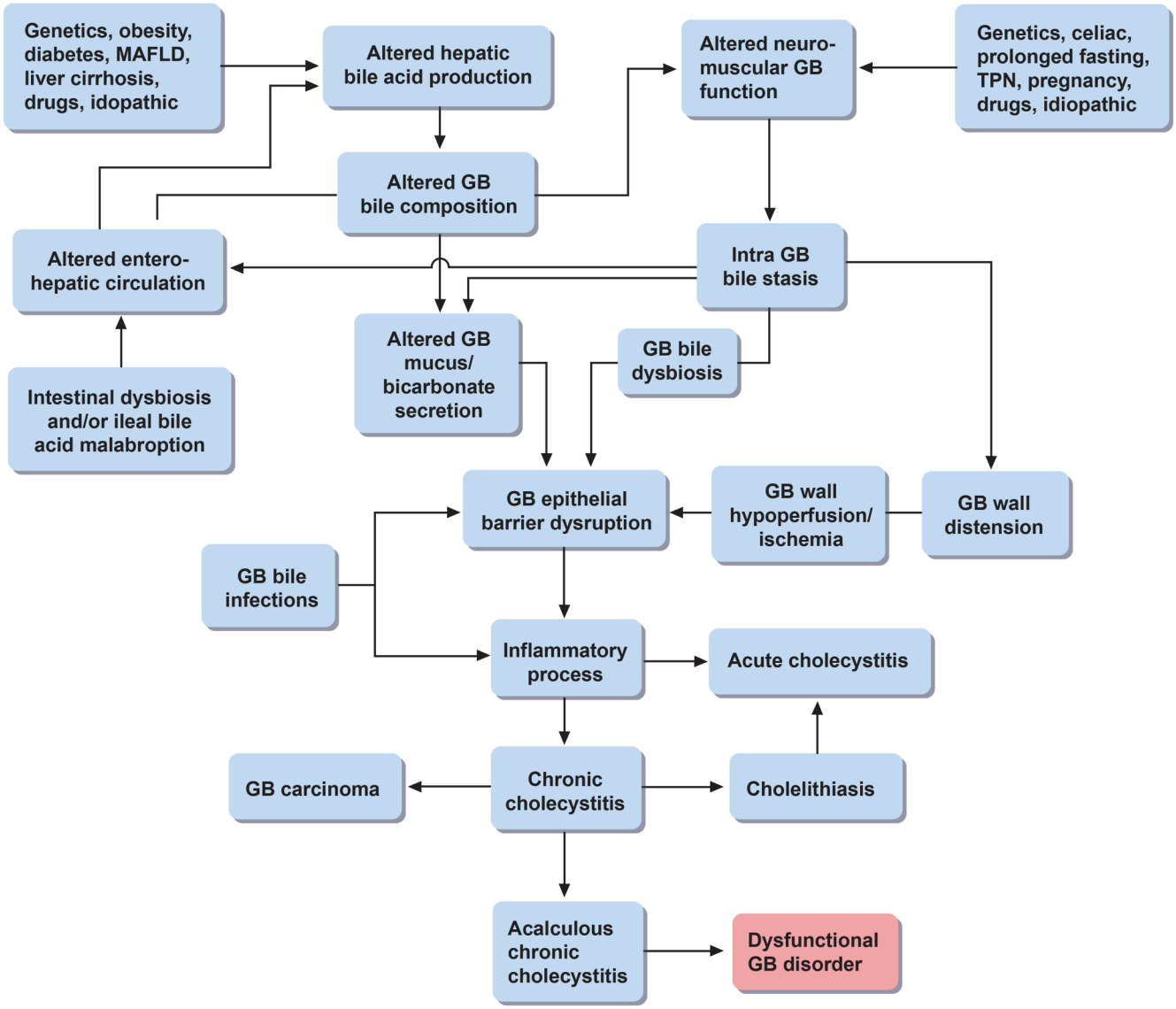

Figure 2. A conceptual model of DGBD pathophysiology.

principle in the pathophysiology of DGBD is the interconnectedness of these 3 factors and their subvariables. For example, GB dysmotility leads to intraluminal bile stasis, which can lead to dysbiosis, GB dilation, and ischemic hypoperfusion of the wall muscle layer, all of which may precipitate altered barrier function and perpetuate epithelial inflammation, leading to further dysmotility. Independent mechanisms that may impact GB contraction include dysregulation of prostaglandin E2, Takeda G protein–coupled receptor 5, and fibroblast growth factor 15. There has been no research on the psychosocial factors that might influence the development, or exacerbate the course of, DGBD. Research in this area is needed to develop effective nonoperative prevention and treatment strategies.

Clinical Evaluation

The diagnostic criteria for dysfunctional gallbladder disorder are listed in Box 2. The possibility of DGBD is considered in patients with typical biliary pain when standard imaging techniques exclude gallstones and other structural pathology of the GB. Laboratory studies that rule out hepatocellular and canalicular liver injury and pancreatic inflammation strengthen confidence in the diagnosis by

Box 2. Diagnostic Criteria for Dysfunctional Gallbladder Disorder

Must include *all* of the following:
1. Typical biliary pain
2. Absence of gallstones or other structural pathology

Supportive criteria:
1. Normal liver enzymes, conjugated bilirubin, and pancreatic enzymes during the pain episode
2. Persistence of symptoms despite a trial of nonoperative therapy

minimizing the likelihood of an alternative pancreaticobiliary etiology. The persistence of symptoms despite a trial period of conservative management may also increase confidence. But overall, the most important criterion in the diagnosis of DGBD is strictly meeting the definition of typical biliary pain, as this is by far most likely to predict response to surgery (see below).

An important change in the diagnostic criteria for DGBD in Rome V is the addition of a supportive criterion that requires the persistence of symptoms throughout a preoperative observation period. This addition is based on expert opinion and some evidence about the natural history of DGBD—that it causes intermittent episodes of biliary pain in a stochastic fashion and will do so for longer than a short period (weeks to months) before abating completely. To minimize unnecessary cholecystectomy and harm, and considering that DGBD is a benign condition that does not result in life-threatening complications, a period of watchful waiting is prudent in most patients to help differentiate patients who might benefit from cholecystectomy from those with more transient symptoms that do not warrant extensive investigation or surgical intervention.

Another important change is the removal of gallbladder ejection fraction (GBEF) from the supportive criteria because the evidence of its ability to predict response to cholecystectomy remains very limited and the presence of typical biliary pain consistently and strongly outperforms cholescintigraphy (CS) as a predictor of response to cholecystectomy.[9–11] However, recognizing that CS is commonly performed in certain parts of the world to justify inappropriate cholecystectomy, the most clinically cogent and evidence-based use of this diagnostic test is addressed below.

The evaluation of patients with typical biliary pain and suspected DGBD is outlined in Figure 3. A detailed history is essential to determine whether symptoms meet the definition of typical biliary pain. Additional testing, including physical examination, laboratory evaluation, cross-sectional imaging, upper endoscopy, gastric-emptying study, and endoscopic ultrasound (EUS), is valuable to exclude other causes of abdominal pain, depending on symptom characteristics. Conditions including peptic ulcer disease, small bowel pathology, gastroparesis, minimal-change chronic pancreatitis, steatotic liver disease, and musculoskeletal syndromes are all within the differential diagnosis of DGBD. In principle, each of these conditions need not be excluded specifically in a patient without suggestive symptoms who meets the definition of typical biliary pain, but whether more intense testing has an appreciable impact on cholecystectomy outcomes remains unclear.

Several imaging methods have been used to measure GB emptying, the most popular of which is CS after pharmacologic stimulation. A small randomized trial, several observation studies, and a meta-analysis suggested that patients with delayed GB emptying benefit from cholecystectomy, although several larger systematic reviews have concluded that there is insufficient evidence to recommend the use of CS.[12–17] One found that although 19 of 23 articles did suggest that GBEF might be useful in selecting patients for cholecystectomy, the methodologic quality of the included studies precluded any recommendations.[13] Importantly, recent systematic reviews have largely observed that clinical response actually occurred in most patients with typical biliary symptoms regardless of emptying parameters.[11,18] Further confounding matters is that a recent study of cholecystectomy candidates with low EF who underwent 2 examinations demonstrated emptying improvement into the normal range in more than one-half of patients.[10]

Overall, existing data on CS are highly inconsistent and subject to bias and confounding and they underscore the importance of high-quality randomized trials to provide clarity in this area.[9] Awaiting such studies, CS does not play a clear role in the diagnosis of DGBD, but it may play a role in surgical decision making in the following 2 groups of patients: (1) those with typical biliary pain and mild-to-moderate symptoms in whom CS results may influence the decision curve around cholecystectomy and (2) those with atypical pain in whom a normal GBEF should strongly discourage cholecystectomy (see below). Based on inadequate evidence, there is currently no role for other imaging modalities for this condition.

Treatment

Although symptomatic calculous disease can progress to serious complications, such as cholecystitis, choledocholithiasis, cholangitis, and acute pancreatitis, DGBD's only clinical manifestations are symptom-related. Thus, the only reason to proceed with cholecystectomy for DGBD is the relief of pain and related symptoms and improved quality of life. In addition, symptoms suggestive of DGBD may resolve spontaneously in up to 50% of cases.[4,11] Because DGBD does not predispose to serious complications and up to one-half of patients may experience symptom resolution without cholecystectomy, early surgical intervention in this patient population is unwarranted. The application of a time delay (eg, 3–6 months) before surgery is a prudent clinical approach that will likely reduce the number of unnecessary cholecystectomies.

In patients who meet criteria for DGBD based on typical biliary pain, if significant symptoms remain after a period of watchful waiting, cholecystectomy is indicated. An interim analysis of a prospective cohort study enrolling patients meeting Rome Criteria for typical biliary pain who underwent cholecystectomy showed an 84%–93% improvement in pain scores and quality of life after resection, underscoring the importance of typical biliary pain in predicting outcome.[18]

At this juncture, in a subset of patients, CS may inform decision making by providing some quantitative prediction of response to surgical intervention. Based on an aforementioned systematic review, when symptoms are typical, complete pain resolution after cholecystectomy is more likely to occur when GBEF is reduced (81% vs 70%; $P = .01$).[11] In addition, patients with typical symptoms and

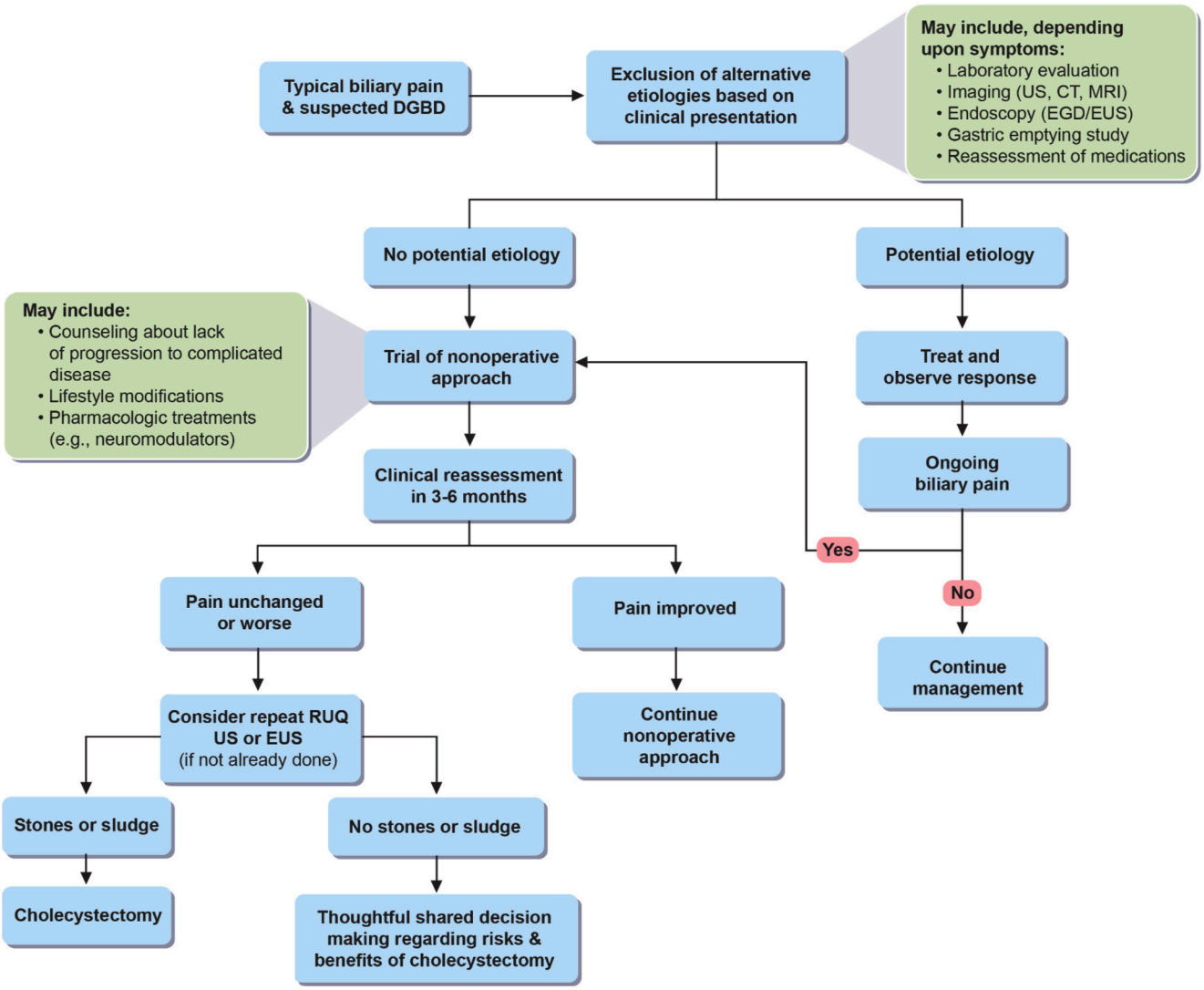

Figure 3. Algorithm for the evaluation of patients with typical biliary pain but no GB stones or other structural abnormalities.

markedly elevated GBEF also seem to experience a high rate of response after cholecystectomy, which could help in decision making.[19] It is important to apply CS only if it is likely to shift the decision curve, as the reported differences in outcomes between patients with typical pain and a low, normal, or high GBEF are relatively small, and thus may have no impact in patients with mild symptoms (who are likely to choose conservative management) and those with severe symptoms (who are likely to favor surgery).

In patients with suspected DGBD who do not meet the definition of typical biliary pain, CS can be considered to stratify those who are least likely to benefit from cholecystectomy. In this context, although outcomes are suboptimal regardless of GBEF, there is evidence to suggest worse outcomes in those with normal GB emptying. For example, patients with atypical symptoms and normal GBEF who underwent cholecystectomy had outcomes similar to those who had nonoperative care.[20] In contrast, a small study of 23 patients with atypical symptoms and a GBEF <35% found that more than one-half responded to cholecystectomy.[18] Thus, for patients with atypical biliary symptoms and a normal GBEF, cholecystectomy is certainly not indicated. If GBEF is low, then cholecystectomy can be contemplated, but thoughtful, shared decision making is mandatory, and additional research is needed.

When considering CS to select patients for cholecystectomy, it is important to apply the aforementioned principles only to patients with pain located in the epigastrium and/or right upper quadrant but absent 1 or more of the additional diagnostic criteria. Patients without upper abdominal pain as a predominant symptom are very unlikely to have a GB disorder and thus should not be candidates for cholecystectomy, regardless of GBEF.

Biliary Sphincter of Oddi Disorder

Definition

Sphincter of Oddi disorder (SOD) is the general term used to define abnormalities of the SO associated with, and possibly causing episodes of biliary pain, elevated liver enzymes, dilation of the bile duct, and attacks of pancreatitis. It is assumed that abnormalities of the biliary

sphincter are more likely to have biliary consequences, and similarly on the pancreatic side; however, motility studies suggest that the 2 can coexist.[21,22]

The following 2 distinct phenotypes are recognized: (1) SO stenosis, which is believed to represent an organic condition caused by fibrosis or inflammation (or both) leading to static obstruction, and (2) SO dyskinesia, which refers to intermittent sphincter spasm. These conditions are not believed to be mutually exclusive. The classic form of SO stenosis is characterized by unequivocal and static evidence of biliary obstruction manifesting as significantly elevated liver tests and a dilated biliary system. The treatment of this condition, which is also typically referred to as ampullary stenosis, is not controversial, as most patients will improve with biliary drainage. In contrast, the less apparent manifestations of SO stenosis and of SO dyskinesia are more difficult to diagnose and treat, and the risk to benefit ratio of ERCP remains uncertain in many patients.

Epidemiology

Up to 40% of patients have persistent or recurrent pain after cholecystectomy.[23] The proportion is higher among patients who had elective rather than emergent surgery, patients without GB stones, and those who also have other nonspecific abdominal symptoms.[23] Results from a meta-analysis including 21 studies comprising 2138 patients showed that gastric pathology was the most common etiology of pain in the first 3 years after cholecystectomy, whereas common bile duct stones were the most common cause after 3 years.[24] In this analysis, SOD accounted for 2%–31% of cases of post-cholecystectomy pain.[24]

SOD generally occurs spontaneously, but has also been described with increased frequency in patients who have undergone liver transplantation,[25] have acquired immunodeficiency syndrome,[26] have hyperlipidemia,[27] and have undergone a Roux-en-Y gastric bypass.[28,29] Chronic opium use has also been implicated as a cause of SOD,[30] although long-standing exposure to opium and narcotic medications commonly results in asymptomatic and clinically unimportant dilation of the biliary tract; thus, the link between opioids and sphincter dysfunction remains unclear.

Recent evidence suggests that although the incidence of SOD is rising, the use of sphincter manometry and sphincterotomy for this condition has decreased in the past decade.[31] The reason for the rising incidence is unclear and may be partly artefactual (eg, increased awareness and better coding), but the concurrent reduction in endoscopic sphincterotomy is attributable to the publication of the EPISOD trial in 2014, which found no benefit associated with sphincterotomy in patients with unexplained upper abdominal pain but no objective evidence of biliary obstruction (see below).[32]

Pathophysiology and Psychological Features

The classic teaching is that aberrant sphincter physiology leads to biliary pain by means of increased resistance to bile outflow and subsequent rise in intrabiliary pressure. SOD has most frequently been described in patients with persistent pain after GB resection (ie, "post-cholecystectomy syndrome"), but whether cholecystectomy is pathophysiologically implicated or whether patients with SOD are simply more likely to have undergone cholecystectomy because of the nature of their symptoms remains unclear. Cholecystectomy has, however, been postulated to unmask pre-existing subclinical SOD by means of removing the reservoir that serves to decompress the extrahepatic biliary system during SO spasm.[33] Furthermore, nerves that travel from the GB to the SO via the cystic duct are severed during cholecystectomy, potentially leading to an imbalance between excitatory and inhibitory input to the SO and altered motility.[34–36] These pathophysiologic hypotheses, however, do not explain SOD in patients with an intact GB, and additional research is necessary to elucidate the true underlying mechanisms.

A fundamental question is whether sphincter hypertension is the proximate driver of symptoms or simply a marker of a more diffuse process, analogous to what has been observed in other DGBI, such as when patients with noncardiac chest pain frequently experience high-amplitude esophageal contractions, but the condition is not adequately treated by long-segment esophageal myotomy.[37] An older study of antroduodenal manometry correlated changes in duodenal motility with spasm of the ampulla of Vater and/or duodenal wall,[38] invoking the possibility that the clinical syndrome ascribed to biliary SOD may be a neuroenteric expression of a separate process (eg, small bowel spasm). This may explain the observation that sphincterotomy can sometimes eliminate future attacks of biliary obstruction without resolution of the pain syndrome.

Other mechanisms, including nociceptive sensitization and cross sensitization with adjacent organs, are likely also at play. Significant tissue inflammation such as cholecystitis will activate nociceptive neurons acutely and, if it persists, can also result in sensitization. In most such patients, cholecystectomy eliminates the ongoing stimulus, and the system quickly reverts to its normal state. However, in a subset of patients (perhaps with a genetically determined vulnerability for neuronal plasticity), the "gain" remains high, even after the GB is removed.[39] In such patients, even minor increases in biliary pressure (within the physiological range) can trigger nociceptive activity and the sensation of pain (allodynia) (Figure 4).

Whether psychological distress is implicated in the pathogenesis of biliary SOD as it is for other DGBI also remains unclear. A small study of 22 patients with suspected biliary SOD (mostly types II and III) who underwent manometry revealed that certain psychological variables, such as stress level, ability to cope with stress, and neuroticism, correlated with SO dyskinesia but not SO stenosis.[40] In contrast, psychological comorbidity was not associated with manometric abnormalities in the EPISOD trial. In comparison, patients in the RESPOnD study—a rigorous prospective cohort of patients undergoing ERCP for SOD—participants were found to have a higher likelihood of underlying anxiety and poor mental health.[41] The

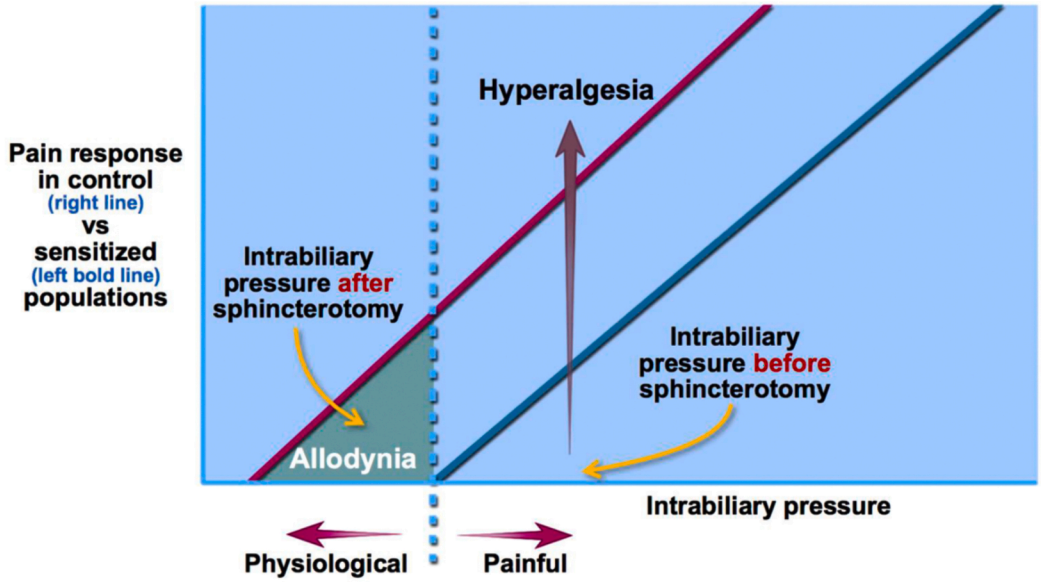

Figure 4. Basic concepts of pain sensitization, as illustrated in a theoretical stimulus-response curve.

reasons for this observed difference between study cohorts are unclear, and whether psychological factors are the culprit in the development of SOD or are simply its consequence remains to be elucidated.

Clinical Evaluation

The diagnostic criteria for biliary sphincter of Oddi disorder are listed in Box 3. Patients with suspected biliary SOD have traditionally been classified according to the modified Milwaukee classification system.[42,43] Type I SOD was defined as biliary-type pain, serum liver enzyme elevations (>1.1 times the upper limit of normal), and biliary dilatation >9 mm. Type II was defined as biliary-type pain with either elevated liver enzymes or biliary dilation. Type III was defined as biliary-type pain without any other objective abnormalities.

This system was embraced in clinical practice primarily because of its perceived ability to predict the outcome of biliary sphincterotomy. However, the landmark EPISOD trial and its long-term follow-up analysis found no medium- or long-term benefit associated with sphincterotomy in patients with suspected type III SOD.[32] Based on this study, as well as the overall evidence, SOD III was abandoned because it does not reflect a primary sphincter disorder. Instead, these patients likely have another DGBI and are best managed as such. In addition, with growing evidence that SOD subtyping does not correlate strongly with outcomes,[41,44] the differentiation between type I and II has also fallen out of favor.

Box 3. Diagnostic Criteria for Biliary Sphincter of Oddi Disorder

Must include *all* of the following:
1. Typical biliary pain
2. Elevated liver tests and/or biliary dilation
3. Absence of bile duct stones or other structural abnormalities

Instead, the term "biliary SOD" is now applied to all patients with biliary-type pain and at least transient evidence of biliary obstruction. Most of these patients experience intermittent SO spasm as the underlying abnormality; however, some with a chronically dilated duct may have an element of sphincter stenosis as well. A subgroup of patients with biliary SOD will have static liver enzyme elevation and biliary dilation (without a stone or mass) and are considered to have a mechanical obstruction or tonic contraction at the level of the SO. In this patient population, the term "SO stenosis" (or "ampullary stenosis") is typically used to denote the structural nature of this disorder and, as above, ERCP in this context is not controversial.

When correlating traditional SOD subtype with the underlying pathophysiological phenotype, it is important to consider that spasm may result in concurrent liver test elevation and bile duct dilation (satisfying criteria for former type I SOD), but it may also result in either elevated liver tests or duct dilation (satisfying criteria for former type II SOD). Thus, it is not accurate to strictly equate SO stenosis to former type I SOD and SO spasm to former type II SOD. This distinction is important because many studies that have been used to inform the response to sphincterotomy were not stratified according to phenotype (stenosis vs spasm) but rather according to SOD subtype (I, II, or III).

The diagnosis and classification of SOD depend in part on bile duct diameter, although the upper limit of normal is controversial and has varied significantly across studies. Although sizes of 6 mm before cholecystectomy and 9 mm after have most commonly been used as the upper limits of normal, a recent, large-scale population-based study of healthy volunteers undergoing abdominal magnetic resonance imaging found that the age-dependent upper reference limit of bile duct diameter is 8 mm in people younger than 65 years and 11 mm in those older than 65 years; this

upper limit of normal increases to 13 mm and 14 mm in the 2 age groups, respectively, after cholecystectomy.[45] This study will need to be replicated in other parts of the world and the effect of this new reference range on predicting response to sphincterotomy will require prospective validation, but the findings may have important implications in the diagnosis and classification of SOD and in selecting patients for ERCP. For example, according to the new reference standard, a 75-year-old patient with biliary-type abdominal pain, normal liver tests, and a prior cholecystectomy, with a bile duct diameter of 11 mm, would not meet the diagnostic criteria for SOD using the new reference standard, although such a patient would have been classified as SOD II in the past.

In Rome V, the supportive criteria for biliary SOD were eliminated. With growing evidence that some patients with biliary SOD can have elevated pancreatic enzymes,[46] the requirement of normal amylase and lipase was removed. Abnormal sphincter manometry was also omitted because of its lack of sensitivity and reproducibility.[47,48] Indeed, manometry was not reproducible or predictive of any outcome in the aforementioned EPISOD trial.[49] Lastly, hepatobiliary scintigraphy was also removed because of the lack of convincing evidence that this test can predict response to sphincterotomy. These changes in the criteria also reflect trends in clinical practice, as both manometry and scintigraphy for SOD have largely been abandoned.

The evaluation of patients with typical biliary pain and suspected biliary SOD is outlined in Figure 5. The initial diagnostic approach should consist of a careful history and physical examination, followed by standard laboratory evaluation and some form of abdominal imaging, with a low threshold for upper endoscopy. Although an ultrasound or computed tomography scan may be used initially, if inconclusive, magnetic resonance cholangiopancreatography (MRCP) and/or EUS provide more complete pancreaticobiliary information. The differential diagnosis includes disorders such as chronic pancreatitis, steatotic liver disease, peptic ulcer disease, musculoskeletal disorders, other rare conditions, and, most commonly, DGBI. The diagnostic approach in patients with an intact GB is similar after the initial exclusion of GB pathology, usually with a transabdominal ultrasound.

Abnormal liver tests in this context could be the result of an independent process, such as a steatotic liver, and as described above, the report of a "dilated bile duct" on imaging tests remains difficult to interpret and is in evolution. In addition, the relevance of other confounding factors, such as bile duct stones at the time of cholecystectomy or opioid use, needs further clarification. Chronic opioid use is a common cause of biliary duct dilation without associated pain or liver enzyme elevation.[50,51] Such patients merit evaluation with EUS or MRCP to exclude occult choledocholithiasis or neoplasm, but biliary SOD should only be invoked if the patient has typical biliary pain.

Once organic causes have been excluded to the greatest extent possible, a noninvasive test that correlates strongly

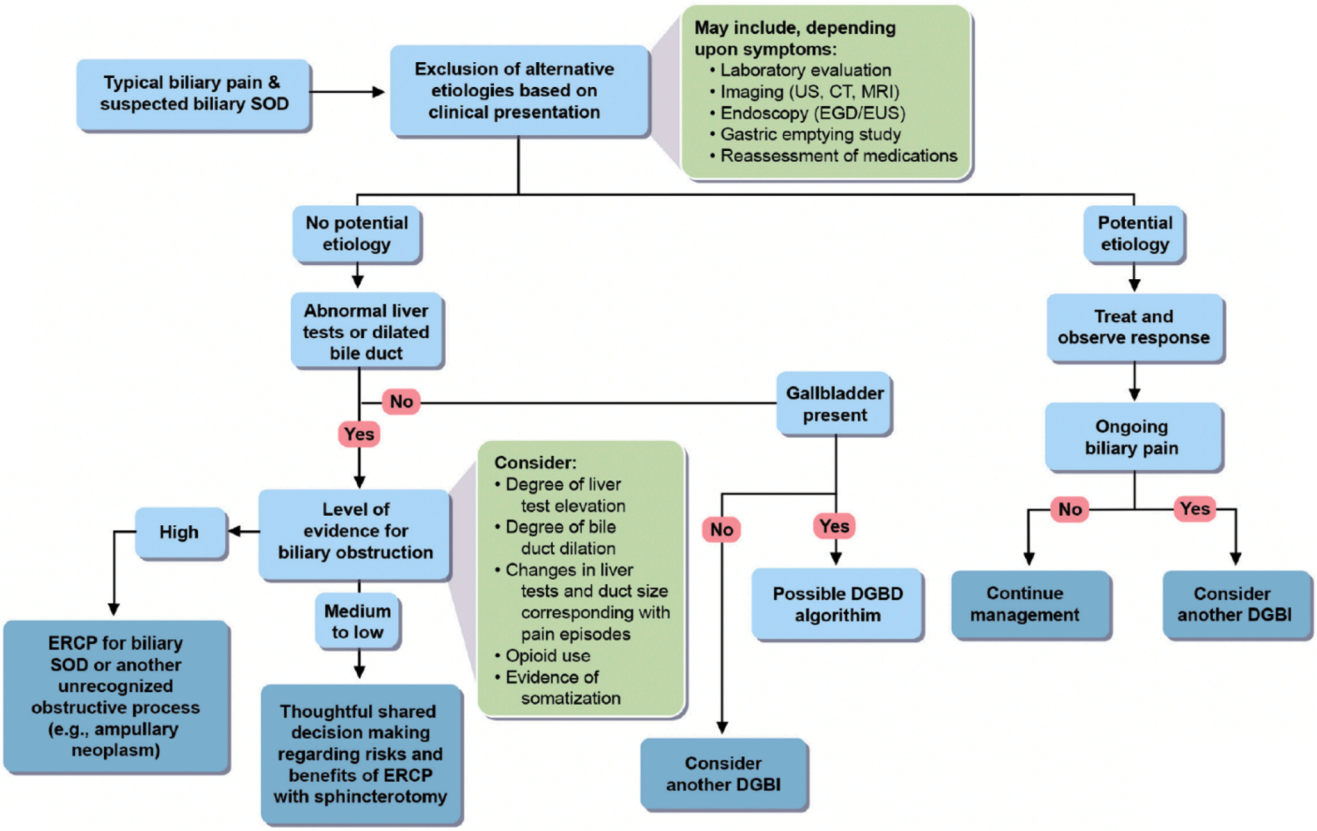

Figure 5. Algorithm for the evaluation of patients with typical biliary pain and suspected biliary SOD.

with response to sphincterotomy would be ideal but remains elusive. A major problem with interpreting this literature is that diagnostic tests have largely been validated against manometry, which is no longer considered the gold standard. The currently available noninvasive tests for biliary SOD, including hepatobiliary scintigraphy and stimulated ultrasound, lack sufficient accuracy to drive clinical decision making and therefore do not play a clear role.

Although SO manometry during ERCP served as the cornerstone for the evaluation of suspected SOD for several decades and was considered the gold standard for some time, this test has now largely been abandoned in clinical practice.[31] Even prior to the reporting of the EPISOD data, the utility of manometry had increasingly come into question because of growing concern over the test's suboptimal performance characteristics.[48] Principally, the sensitivity of manometry was questioned because of concern that short-term measurement of sphincter pressure is inadequate for detecting intermittent spasm that is not occurring at the time of the procedure. In addition, studies have found that repeat manometry may be abnormal in 40%–60% of persistently symptomatic patients with an initially normal result.[47] As mentioned, manometry was not reproducible or clinically predictive of any outcome in the EPISOD trial.[49]

Alternative methods of diagnosing SOD that have been proposed include placement of an endoprosthesis on a trial basis, as well as injection of botulinum toxin into the SO. Although preliminary data have suggested the utility of diagnostic stent placement, the need for multiple risky procedures limits its widespread application. Botulinum toxin injection into the SO was found in an exploratory study to reduce clinically significant fistula formation after distal pancreatectomy, implicating sphincter hypertension in the pathogenesis of this complication and suggesting that temporary paralysis of the SO can result in therapeutic benefit.[52] Whether this observation can be extrapolated to the diagnosis and treatment of SOD requires further study. Given the preliminary evidence that ampullary botulinum toxin injection is safe, well-designed prospective studies may be of value.

Treatment

Given the risks of ERCP, pharmacotherapy to reduce sphincter pressures is attractive but underinvestigated in rigorous studies. Several drugs, nerve stimulation, and acupuncture have been found to reduce SO pressures, although rigorous clinical outcomes data are lacking. Short-term placebo-controlled crossover studies found that 75% of patients with suspected or documented SOD experienced statistically less pain with the use of oral nifedipine.[53] A subsequent study, however, found that slow-release nifedipine provided no benefit but did increase cardiovascular adverse effects.[54] A prospective study of nitrates published only in abstract form showed some reduction in pain, but therapy was limited by adverse effects.[55] A French group was able to avoid sphincterotomy in 77% of patients with suspected SOD using medical treatment with trimebutine and nitrates.[56]

As discussed, however, most patients who have traditionally been referred for suspected SOD likely have another DGBI and/or have some element of visceral hyperalgesia and may benefit from neuromodulation and/or antispasmodic therapy more so than from sphincter-directed therapy. For example, in a small exploratory study, patients with mostly type III SOD experienced a promising response to a 12-week trial of duloxetine.[57] A prior uncontrolled study of mostly patients with SOD II reported better outcomes with medical management (mostly amitriptyline) compared with sphincterotomy.[58] Currently, medical management directed at the sphincter or the enteric nervous system (or both) does not have a primary role for suspected biliary SOD.

Endoscopic biliary sphincterotomy remains the primary modality to treat suspected SO stenosis and spasm and is commonly used in clinical practice. Studies from the era in which manometry was commonly performed for SOD found that abdominal pain is relieved after sphincterotomy in >90% of patients with traditional type I biliary SOD, regardless of documented sphincter hypertension. The evidence supporting sphincterotomy in patients with less concrete evidence of biliary obstruction (prior SOD type II) is not strong; most studies have been retrospective and open-label and have used subjective outcome measures.

A better understanding of predictors of response to endoscopic sphincterotomy is critical. A retrospective study of 121 patients showed that normal pancreatic manometry, delayed gastric emptying, daily opioid use, and age younger than 40 years predicted worse outcomes, but found no difference between the 3 SOD types.[44] It has also been reported that patients were more likely to respond if their pain was intermittent (not continuous), if it was accompanied by nausea and vomiting, and if there was a pain-free interval of at least 1 year after cholecystectomy.[59] A recent methodologically rigorous multicenter prospective cohort study of 213 patients undergoing ERCP for a suspected SOD—the aforementioned RESPOnD study—also failed to find an association between SOD subtype and response to ERCP,[41] affirming that the previous phenotyping paradigm for SOD—based on liver tests and bile duct size alone—is inadequate. This evidence underscores the importance of expanding the focus of future research to a broader range of possible predictors, including psychosocial factors and other DGBI, among others.

The large majority of existing evidence informs the approach to SOD in patients after cholecystectomy, which, as above, has been postulated to unmask SOD by removing the reservoir effect[33] and/or lead to altered SO motility by severing inhibitory nerves that travel via the cystic duct.[34] Very limited data, in contrast, suggest that SOD may occur in patients with an intact GB. A small case series of patients with documented SO hypertension and an intact GB who were treated with sphincterotomy reported that 43% had long-term pain relief, and some additional patients eventually improved after cholecystectomy.[60] In the RESPOnD study, participants with an intact GB had a similar response rate to that of the overall cohort.[41] For all intents and purposes, however, the clinical approach does not differ

materially according to the presence or absence of a GB other than the first step of assessing for GB stones.

When a patient with suspected biliary SOD does not respond to biliary sphincterotomy, the most likely explanation is that the pain was not of pancreaticobiliary origin but was caused instead by another DGBI. However, in some cases, the biliary sphincterotomy may have been inadequate, or restenosis may have occurred. ERCP after a prior biliary sphincterotomy, which should have separated the biliary from the pancreatic orifice, is associated with a lower risk of post-ERCP pancreatitis and is thus justified in patients with a significant prior response, although there is no evidence of rigorously studying outcomes in this context.

In contrast to DGBD, for which the presence of typical biliary pain is a strong predictor of response to cholecystectomy, the importance of typical biliary pain in decision making around biliary SOD is less certain. This may be in part because endoscopic research has not been as rigorous as the surgical literature in stratifying response according to symptom complex, or because, as discussed previously, some forms of sphincter dysfunction result in more static obstruction that may manifest with a less typical pain pattern.

On this basis, and as we await better data, the decision to proceed with ERCP in patients with suspected biliary SOD but atypical pain should be driven primarily by the balance between the degree of biliary obstruction and the presence of confounders that might predict a lower likelihood of response. For example, a patient with atypical pain (or no pain at all) and static evidence of significant biliary obstruction (eg, jaundice and duct dilation) but no clear obstructive cause (ie, a mass or stone) merits ERCP. In contrast, ERCP is unlikely to be beneficial in a patient with atypical pain, bile duct dilation, and chronic opioid use.

Pancreatic Sphincter of Oddi Disorder

Definition

It had traditionally been believed that SOD can cause pancreatic pain in the absence of acute or chronic pancreatitis. However, there is no evidence to support this contention. Indeed, dilated pancreatic ducts are rare in patients with "unexplained epigastric pain" and are more likely due to chronic pancreatitis or main duct intraductal papillary mucinous neoplasm. In addition, elevations of amylase and lipase can occur in healthy individuals or in patients with nonpancreatic abdominal pain. For these reasons and considering the short- and long-term risks of ERCP with pancreatic sphincterotomy, the diagnosis of pancreatic SOD is now limited to patients with unexplained RAP. The fundamental premise is that pancreaticobiliary sphincter dysfunction or stenosis can lead to transient elevation in pancreatic duct pressures, which can induce pancreatic inflammation, akin to gallstone pancreatitis.

Based on the current Rome V diagnostic criteria, the diagnosis of pancreatic SOD is functionally synonymous with unexplained RAP (also known as idiopathic RAP), although pancreatic SOD represents only a subset of unexplained RAP because a sphincter disorder is likely to be the culprit in only a minority of such cases. This misalignment underscores the importance of identifying predictors of response to sphincterotomy, such that the definition of pancreatic SOD (and its treatment implications) can be applied to those who have a bona fide sphincter disorder, not all patients with unexplained RAP. In the interim, however, toward the overall goal of restricting the use of ERCP to those who are most likely to benefit, pancreatic SOD should only be invoked in patients with RAP. ERCP may have a role in patients with pancreatic duct dilation in the absence of acute pancreatitis, although it should be recognized that, based on available evidence, these patients are more likely to have chronic pancreatitis or main duct intraductal papillary mucinous neoplasm rather than pancreatic ampullary stenosis.

An additional important consideration is that even though the disorder's name implicates the pancreatic component of the sphincter complex, it remains unclear whether outflow obstruction occurs primarily at the pancreatic sphincter, more downstream at the level of the common sphincter, or both. Therefore, pancreatic SOD is so-named more for its principal manifestation (ie, attacks of pancreatitis) rather than for its pathophysiology, which is yet to be fully elucidated.

Epidemiology

The epidemiology and natural history of RAP and idiopathic RAP are reasonably well-defined, although very little is known about the subgroup of patients with pancreatic SOD. Among patients with idiopathic RAP, sphincter hypertension has been observed in 25%–75% in case series from referral centers.[61] Early small studies suggested that the majority of patients in whom the suspected cause of RAP is SOD are women in their 40s—a sex and age distribution similar to that observed with biliary SOD.[62]

Given the natural history of RAP, episodes of pain may occur at intervals of months (or years) rather than days, and in most instances the recurrences are less severe than the index attack of pancreatitis.

Pathophysiology and Psychological Features

Obstruction at the level of the SO is well known to cause pancreatitis in animal models and in several clinical scenarios, most commonly gallstone pancreatitis. In addition, some medications, including conventional opioids and eluxadoline (a μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist), can induce sphincter spasm and have been implicated in the pathogenesis of biliary-type abdominal pain and acute pancreatitis in patients without a GB.[63] It is therefore reasonable to postulate that overactivity of the sphincter muscle could cause pancreatitis due to fluctuations in intraductal pressures. However, in contrast to biliary sphincter dysfunction, for which evidence supporting the proposed mechanisms of disease exists (discussed above), there is little physiologic explanation for why the pancreatic sphincter should become dysfunctional. One possible explanation is that inflammation and subsequent fibrosis related to an initial attack of acute pancreatitis (regardless of etiology) or underlying chronic pancreatitis can involve or

"spill over" to the pancreatic sphincter, which then contributes to the pathogenesis of subsequent attacks. Long-term follow-up of patients with unexplained RAP revealed the development of chronic pancreatitis in a sizable fraction of patients.[64,65] This progression might be caused by the attacks themselves, which occur with increasing frequency as the sphincter accumulates more injury. Alternatively, the recurrent attacks of acute pancreatitis may simply be a manifestation of the natural history of the underlying chronic pancreatitis, and any apparent sphincter abnormality is simply the consequence of the adjacent fibroinflammatory process rather than a primary driver of disease.

As with biliary SOD, it remains unclear whether psychological factors can contribute to abnormalities in sphincter function. Although there are extensive data on the psychological burden inflicted by RAP, none of these are specific to the subset of patients with a sphincter disorder.

Clinical Evaluation

The diagnostic criteria for pancreatic sphincter of Oddi disorder are listed in Box 4. The pancreatitis episodes should meet standard diagnostic criteria, satisfying at least 2 of the following 3 features: typical pain consistent with acute pancreatitis; pancreatic enzyme elevations greater than 3 times the upper limit of normal; and characteristic imaging showing pancreatic inflammation.[66] The label of unexplained RAP is applied after ruling out other known causes of acute pancreatitis listed in Box 4. However, despite thorough and thoughtful evaluation, attribution of RAP to a specific etiology may remain challenging or impossible, particularly as it relates to essential medications, cigarette smoking, and genetic testing. Many patients referred for evaluation of RAP are smokers, take essential or salutary medications that are loosely associated with acute pancreatitis, and/or have identifiable mutations of pancreatitis-facilitating genes. It remains unknown whether such patients should be excluded from a possible diagnosis of pancreatic SOD, and some experts offer ERCP.

In Rome V, the requirement of a negative EUS (former criterion 3) was removed because, generally speaking, EUS is necessary to satisfy criterion 2 (other etiologies of pancreatitis excluded). In addition, although EUS is considered the preferred diagnostic test for unexplained RAP, MRCP is a reasonable complementary or alternative test based on local expertise and availability. In addition, as in the case of biliary SOD, the requirement of abnormal sphincter manometry was eliminated as a diagnostic criterion because of its lack of sensitivity and reproducibility.[47,48,67] On this basis, and for other logistic and safety reasons, manometry has been essentially abandoned for this indication and overall.

Box 4. Diagnostic Criteria for Pancreatic Sphincter of Oddi Disorder

Must include both the following:
1. Documented recurrent episodes of acute pancreatitis
2. Other etiologies of pancreatitis excluded[a]

[a]Gallstones, alcohol, hypertriglyceridemia, autoimmune, hypercalcemia, medications, pancreatic mass, ampullary lesion, pancreas divisum, anomalous pancreaticobiliary junction, genetic, and acute exacerbation of underlying chronic pancreatitis.

The main diagnostic objective in patients with suspected pancreatic SOD is to exclude other etiologies of acute pancreatitis. This remains a major challenge in clinical practice as the cause remains unclear in up to 30% of cases, despite an extensive evaluation.[68] Although a detailed history and physical examination, as well as transabdominal ultrasound and computed tomography, play an important role, EUS has become the principal diagnostic modality for the evaluation of unexplained RAP, with a yield ranging from approximately 30% to 90%.[68] The purpose of EUS in this context is to assess for anatomic abnormalities in the pancreaticobiliary system that may predispose to or cause pancreatitis, such as occult stones or sludge in the GB or bile duct, unrecognized pancreatic or ampullary neoplasms, pancreatic ductal abnormalities, or chronic pancreatitis. EUS most commonly identifies occult biliary stone disease but ampullary or pancreatobiliary malignancy may be observed in up to 5% of patients after 1 episode of unexplained pancreatitis and in 12% of those with RAP.[68]

Existing evidence, including prospective comparative analyses, indicates that EUS is more likely than MRCP to establish a probable cause of pancreatitis.[69] In addition, EUS allows direct endoscopic visualization of the papilla to exclude a neoplasm at this location. However, the diagnostic yield of magnetic resonance imaging is also high, and this modality can be particularly helpful in identifying pancreatic ductal etiologies such as pancreas divisum or anomalous pancreaticobiliary union. Most often, MRCP is used as a complementary test when EUS is unrevealing, but it is a reasonable alternative examination when EUS is unavailable, and some experts insist on both to more definitively establish the diagnosis of pancreatic SOD.[68]

Objective measurement of pancreatic duct size by MRCP before and after intravenous administration of secretin is an attractive method of diagnosing pancreatic SOD, and small prospective studies have shown the potential to select patients who would benefit from endotherapy.[68] Another study suggested that although secretin MRCP revealed dynamic duct size changes in patients with suspected pancreatic SOD, the results did not predict sphincterotomy outcome.[70] This test deserves further assessment, although progress has been slow.

Treatment

Given the lack of strong evidence supporting ERCP for pancreatic SOD, and the risks of the procedure, a trial of conservative management and watchful waiting are always reasonable in patients who have not demonstrated that their RAP will follow an aggressive clinical course. Although certain medications (such as antispasmodics and calcium channel blockers) are known to relax the sphincter, there

have been no trials assessing their value in this context. Pancreatic enzyme supplements have been used to reduce pain in patients with chronic pancreatitis (with conflicting data) but have not been studied in recurrent pancreatitis. The same applies to dietary antioxidant therapy.

Observational studies have suggested that further attacks of recurrent pancreatitis can be prevented by sphincterotomy in 60%–80% of patients. A small, open-label randomized trial demonstrated that pancreatic duct stent placement reduced RAP from 53% to 11% ($P < .02$) compared with medical therapy alone.[71] Another observational study with 6- to 10-year follow-up also suggested a benefit of approximately 50% associated with sphincterotomy.[72] A prospective evaluation of 8 patients with RAP due to SOD who underwent sphincterotomy showed a 75% response through approximately 3 years of follow-up.[73] Conversely, a retrospective study with a median follow-up of 7 years suggested that sphincterotomy had no effect.[74] In the RESPOND study, the rate of recurrent pancreatitis in patients with RAP undergoing sphincterotomy was similar to that of historical controls who did not undergo intervention.[41]

Another relevant consideration is the role of ERCP with minor papillotomy for patients with RAP and pancreas divisum—an area for which rigorous studies have been lacking and conflicting. Although this condition is not considered a sphincter disorder (as the minor papilla does not comprise a true anatomic sphincter), the imbalance between the volume of flow through the dominant dorsal system and the small size of the minor papilla has been implicated as a cause of increased intraductal pressure, the same putative mechanism of disease as pancreatic SOD. The SHARP (Sphincterotomy for Acute Recurrent Pancreatitis) trial—an international, multicenter, randomized, sham-controlled trial evaluating minor papilla sphincterotomy in patients with pancreas divisum and RAP—recently reported no benefit associated with ERCP.[75] This lack of benefit despite presumed improvement of pancreatic outflow significantly dampens the enthusiasm for sphincterotomy in patients with standard pancreatic ductal anatomy.

One limitation of the literature is that the approach to endoscopic therapy in published studies has been highly variable. One or more of the following strategies have been used: biliary and/or pancreatic manometry-guided treatment; biliary, pancreatic, and dual sphincterotomy; dilation; and stent placement. Thus, it remains unclear whether the absence of clear benefit in the literature is because sphincter dysfunction is not an etiologic factor or because the optimal treatment approach has not been defined and/or applied consistently. The aforementioned observational study with a more than 10-year follow-up and another study published only in abstract form found that biliary sphincterotomy alone was not nearly as effective as dual or pancreatic sphincterotomy, suggesting that the pancreatic sphincter is specifically culprit. A subsequent randomized trial suggested that biliary sphincterotomy alone (which also reduces pancreatic duct pressure by ablating the common sphincter) yields outcomes equivalent to dual sphincterotomy in patients with abnormal pancreatic manometry.[76] This observation is appealing because pancreatic sphincterotomy carries a higher risk of acute and long-term complications, including papillary restenosis, which can occasionally follow a relentless course that is significantly worse than the original problem. Therefore, many endoscopists now perform empiric biliary sphincterotomy alone at the time of the first ERCP and only consider pancreatic endotherapy for inadequate response.

Randomized trials are required to determine whether sphincterotomy is effective for pancreatic SOD and, if so, what approach is preferred (ie, biliary, pancreatic, or dual sphincterotomy). In the absence of well-designed trials, the decision to proceed should be individualized, considering factors such as the patient's disease burden and the potential for iatrogenic complications.

Conclusions

Rome V aims to better define biliary pain, provide improved diagnostic criteria for DGBD and biliary and pancreatic SO disorders, and updates guidance on diagnosis and therapy. Unfortunately, many of the conclusions continue to be based on expert opinion due to a lack of conclusive evidence, but the following research priorities would be most impactful: (1) clinical trials of cholecystectomy vs sham or medical management (or both) in patients with atypical biliary pain, stratified by GBEF; (2) mechanistic studies elucidating the connection between foregut dysmotility and/or hypersensitivity and SO dysfunction; (3) large-scale observational studies or pilot randomized controlled trials of pharmacotherapy and botulinum toxin injection for suspected biliary SOD; (4) sham-controlled trials of endoscopic sphincterotomy for patients with suspected biliary SOD; (5) large-scale observational studies of predictors of response to endoscopic sphincterotomy among patients with suspected biliary and pancreatic SOD; (6) sham-controlled trials of endoscopic sphincterotomy for patients with suspected pancreatic SOD; and (7) studies investigating the psychological features of DGBD, biliary SOD, and pancreatic SOD, and whether modifying psychological factors can impact disease course.

References

1. Doran FS. The sites to which pain is referred from the common bile-duct in man and its implication for the theory of referred pain. Br J Surg 1967;54:599–606.
2. Kingham JG, Dawson AM. Origin of chronic right upper quadrant pain. Gut 1985;26:783–788.
3. Chapman WP, Herrera R, Jones CM. A comparison of pain produced experimentally in lower esophagus, common bile duct, and upper small intestine with pain experienced by patients with diseases of biliary tract and pancreas. Surg Gynecol Obstet 1949;89:573–582.
4. Bielefeldt K, Saligram S, Zickmund SL, et al. Cholecystectomy for biliary dyskinesia: how did we get there? Dig Dis Sci 2014;59:2850–2863.

5. Kaye AJ, Jatla M, Mattei P, et al. Use of laparoscopic cholecystectomy for biliary dyskinesia in the child. J Pediatr Surg 2008;43:1057–1059.
6. Preston JF, Diggs BS, Dolan JP, et al. Biliary dyskinesia: a surgical disease rarely found outside the United States. Am J Surg 2015;209:799–803; discussion 803.
7. The epidemiology of gallstone disease in Rome, Italy. Part I. Prevalence data in men. The Rome Group for Epidemiology and Prevention of Cholelithiasis (GREPCO). Hepatology 1988;8:904–906.
8. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation Global Study. Gastroenterology 2021;160:99–114.e3.
9. DiBaise JK, Richmond BK, Ziessman HH, et al. Cholecystokinin-cholescintigraphy in adults: consensus recommendations of an interdisciplinary panel. Clin Gastroenterol Hepatol 2011;9:376–384.
10. Rose JB, Fields RC, Strasberg SM. Poor reproducibility of gallbladder ejection fraction by biliary scintigraphy for diagnosis of biliary dyskinesia. J Am Coll Surg 2018; 226:155–159.
11. Alhayo S, Eslick GD, Cox MR. Cholescintigraphy may have a role in selecting patients with biliary dyskinesia for cholecystectomy: a systematic review. ANZ J Surg 2020;90:1647–1652.
12. Delgado-Aros S, Cremonini F, Bredenoord AJ, et al. Systematic review and meta-analysis: does gall-bladder ejection fraction on cholecystokinin cholescintigraphy predict outcome after cholecystectomy in suspected functional biliary pain? Aliment Pharmacol Ther 2003; 18:167–174.
13. DiBaise JK, Oleynikov D. Does gallbladder ejection fraction predict outcome after cholecystectomy for suspected chronic acalculous gallbladder dysfunction? A systematic review. Am J Gastroenterol 2003; 98:2605–2611.
14. Sabbaghian MS, Rich BS, Rothberger GD, et al. Evaluation of surgical outcomes and gallbladder characteristics in patients with biliary dyskinesia. J Gastrointest Surg 2008;12:1324–1330.
15. Paajanen H, Miilunpohja S, Joukainen S, et al. Role of quantitative cholescintigraphy for planning laparoscopic cholecystectomy in patients with gallbladder dyskinesia and chronic abdominal pain. Surg Laparosc Endosc Percutan Tech 2009;19:16–19.
16. Ponsky TA, DeSagun R, Brody F. Surgical therapy for biliary dyskinesia: a meta-analysis and review of the literature. J Laparoendosc Adv Surg Tech A 2005; 15:439–442.
17. Mahid SS, Jafri NS, Brangers BC, et al. Meta-analysis of cholecystectomy in symptomatic patients with positive hepatobiliary iminodiacetic acid scan results without gallstones. Arch Surg 2009;144:180–187.
18. Carr JA, Walls J, Bryan LJ, et al. The treatment of gallbladder dyskinesia based upon symptoms: results of a 2-year, prospective, nonrandomized, concurrent cohort study. Surg Laparosc Endosc Percutan Tech 2009; 19:222–226.
19. Kartik A, Jorge IA, Webb C, et al. Defining biliary hyperkinesia and the role of cholecystectomy. J Am Coll Surg 2023;237:706–710.
20. Gudsoorkar VS, Oglat A, Jain A, et al. Systematic review with meta-analysis: cholecystectomy for biliary dyskinesia-what can the gallbladder ejection fraction tell us? Aliment Pharmacol Ther 2019;49:654–663.
21. Chan YK, Evans PR, Dowsett JF, et al. Discordance of pressure recordings from biliary and pancreatic duct segments in patients with suspected sphincter of Oddi dysfunction. Dig Dis Sci 1997;42:1501–1506.
22. Raddawi HM, Geenen JE, Hogan WJ, et al. Pressure measurements from biliary and pancreatic segments of sphincter of Oddi. Comparison between patients with functional abdominal pain, biliary, or pancreatic disease. Dig Dis Sci 1991;36:71–74.
23. Vetrhus M, Berhane T, Soreide O, et al. Pain persists in many patients five years after removal of the gallbladder: observations from two randomized controlled trials of symptomatic, noncomplicated gallstone disease and acute cholecystitis. J Gastrointest Surg 2005; 9:826–831.
24. Isherwood J, Oakland K, Khanna A. A systematic review of the aetiology and management of post cholecystectomy syndrome. Surgeon 2019;17:33–42.
25. Rerknimitr R, Sherman S, Fogel EL, et al. Biliary tract complications after orthotopic liver transplantation with choledochocholedochostomy anastomosis: endoscopic findings and results of therapy. Gastrointest Endosc 2002;55:224–231.
26. Cello JP, Chan MF. Long-term follow-up of endoscopic retrograde cholangiopancreatography sphincterotomy for patients with acquired immune deficiency syndrome papillary stenosis. Am J Med 1995;99:600–603.
27. Szilvassy Z, Nagy I, Madacsy L, et al. Beneficial effect of lovastatin on sphincter of Oddi dyskinesia in hypercholesterolemia and hypertriglyceridemia. Am J Gastroenterol 1997;92:900–902.
28. Schwartz PB, Easler JJ, Lancaster WP, et al. Sphincter of Oddi dysfunction after gastric bypass: surgical or endoscopic therapy? J Surg Res 2019;238:41–47.
29. May D, Vogels E, Parker D, et al. Overall outcomes of laparoscopic-assisted ERCP after Roux-en-Y gastric bypass and sphincter of Oddi dysfunction subgroup analysis. Endosc Int Open 2019;7:E1276–E1280.
30. Sharma SS. Sphincter of Oddi dysfunction in patients addicted to opium: an unrecognized entity. Gastrointest Endosc 2002;55:427–430.
31. Smith ZL, Shah R, Elmunzer BJ, et al. The Next EPISOD: trends in utilization of endoscopic sphincterotomy for sphincter of Oddi dysfunction from 2010-2019. Clin Gastroenterol Hepatol 2022;20:e600–e609.
32. Cotton PB, Durkalski V, Romagnuolo J, et al. Effect of endoscopic sphincterotomy for suspected sphincter of Oddi dysfunction on pain-related disability following cholecystectomy: the EPISOD randomized clinical trial. JAMA 2014;311:2101–2109.
33. Lisbona R. The scintigraphic evaluation of sphincter of Oddi dysfunction. J Nucl Med 1992;33:1223–1224.

34. Luman W, Williams AJ, Pryde A, et al. Influence of cholecystectomy on sphincter of Oddi motility. Gut 1997;41:371–374.
35. Middelfart HV, Matzen P, Funch-Jensen P. Sphincter of Oddi manometry before and after laparoscopic cholecystectomy. Endoscopy 1999;31:146–151.
36. Fan MM, Li F, Zhang XW. Changes of the sphincter of Oddi motility in dog after cholecystectomy. J Dig Dis 2012;13:40–46.
37. Patti MG, Gorodner MV, Galvani C, et al. Spectrum of esophageal motility disorders: implications for diagnosis and treatment. Arch Surg 2005;140:442–448; discussion 448–449.
38. Koussayer T, Ducker TE, Clench MH, et al. Ampulla of Vater/duodenal wall spasm diagnosed by antroduodenal manometry. Dig Dis Sci 1995;40:1710–1719.
39. Pasricha PJ. Unraveling the mystery of pain in chronic pancreatitis. Nat Rev Gastroenterol Hepatol 2012; 9:140–151.
40. Bennett E, Evans P, Dowsett J, et al. Sphincter of Oddi dysfunction: psychosocial distress correlates with manometric dyskinesia but not stenosis. World J Gastroenterol 2009;15:6080–6085.
41. Cote GA, Elmunzer BJ, Nitchie H, et al. Sphincterotomy for biliary sphincter of Oddi disorder and idiopathic acute recurrent pancreatitis: the RESPOnD longitudinal cohort. Gut 2024;74:58–66.
42. Hogan WJ, Geenen JE. Biliary dyskinesia. Endoscopy 1988;20(Suppl 1):179–183.
43. Geenen JE, Rolny P. Endoscopic therapy of acute and chronic pancreatitis. Gastrointest Endosc 1991;37:377–382.
44. Freeman ML, Gill M, Overby C, et al. Predictors of outcomes after biliary and pancreatic sphincterotomy for sphincter of Oddi dysfunction. J Clin Gastroenterol 2007;41:94–102.
45. Beyer G, Kasprowicz F, Hannemann A, et al. Definition of age-dependent reference values for the diameter of the common bile duct and pancreatic duct on MRCP: a population-based, cross-sectional cohort study. Gut 2023;72:1738–1744.
46. Cote GA, Nitchie H, Elmunzer BJ, et al. Characteristics of patients undergoing endoscopic retrograde cholangiopancreatography for sphincter of Oddi disorders. Clin Gastroenterol Hepatol 2022;20:e627–e634.
47. Khashab MA, Watkins JL, McHenry L Jr, et al. Frequency of sphincter of Oddi dysfunction in patients with previously normal sphincter of Oddi manometry studies. Endoscopy 2010;42:369–374.
48. Viceconte G, Micheletti A. Endoscopic manometry of the sphincter of Oddi: its usefulness for the diagnosis and treatment of benign papillary stenosis. Scand J Gastroenterol 1995;30:797–803.
49. Suarez AL, Pauls Q, Durkalski-Mauldin V, Cotton PB. Sphincter of Oddi manometry: reproducibility of measurements and effect of sphincterotomy in the EPISOD Study. J Neurogastroenterol Motil 2016;22:477–482.
50. Zylberberg H, Fontaine H, Correas JM, et al. Dilated bile duct in patients receiving narcotic substitution: an early report. J Clin Gastroenterol 2000;31:159–161.
51. Sunkara T, Gorrepati VS, Yarlagadda KS, et al. Methadone use and asymptomatic common bile duct dilation: re-examining the link. Neth J Med 2018;76:207–209.
52. Hackert T, Klaiber U, Hinz U, et al. Sphincter of Oddi botulinum toxin injection to prevent pancreatic fistula after distal pancreatectomy. Surgery 2017;161:1444–1450.
53. Sand J, Nordback I, Koskinen M, et al. Nifedipine for suspected type II sphincter of Oddi dyskinesia. Am J Gastroenterol 1993;88:530–535.
54. Craig AG, Toouli J. Slow release nifedipine for patients with sphincter of Oddi dyskinesia: results of a pilot study. Intern Med J 2002;32:119–120.
55. Cuer JC, Abergel A, Dapoigny M, et al. The efficacy of glycerol trinitrate in patients with sphincter of Oddi dysfunction. A prospective double-blind study. Gastroenterology 1995;108:A412.
56. Vitton V, Delpy R, Gasmi M, et al. Is endoscopic sphincterotomy avoidable in patients with sphincter of Oddi dysfunction? Eur J Gastroenterol Hepatol 2008;20:15–21.
57. Pauls Q, Durkalski-Mauldin V, Brawman-Mintzer O, et al. Duloxetine for the treatment of patients with suspected sphincter of Oddi dysfunction: a pilot study. Dig Dis Sci 2016;61:2704–2709.
58. Kalaitzakis E, Ambrose T, Phillips-Hughes J, et al. Management of patients with biliary sphincter of Oddi disorder without sphincter of Oddi manometry. BMC Gastroenterol 2010;10:124.
59. Topazian M, Hong-Curtis J, Li J, et al. Improved predictors of outcome in postcholecystectomy pain. J Clin Gastroenterol 2004;38:692–696.
60. Choudhry U, Ruffolo T, Jamidar P, et al. Sphincter of Oddi dysfunction in patients with intact gallbladder: therapeutic response to endoscopic sphincterotomy. Gastrointest Endosc 1993;39:492–495.
61. Petersen 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; 59:670–687.
62. Toouli J. The sphincter of Oddi and acute pancreatitis–revisited. HPB (Oxford) 2003;5:142–145.
63. Cash BD, Lacy BE, Watton C, et al. Post-marketing reports of pancreatitis in eluxadoline-treated patients pre and post US label change. Therap Adv Gastroenterol 2021;14:17562848211001725.
64. Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. Am J Gastroenterol 2012;107:1096–1103.
65. Lankisch PG, Breuer N, Bruns A, et al. Natural history of acute pancreatitis: a long-term population-based study. Am J Gastroenterol 2009;104:2797–2805; quiz 2806.
66. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–111.
67. Varadarajulu S, Hawes RH, Cotton PB. Determination of sphincter of Oddi dysfunction in patients with prior normal manometry. Gastrointest Endosc 2003; 58:341–344.

68. Strand DS, Law RJ, Yang D, et al. AGA clinical practice update on the endoscopic approach to recurrent acute and chronic pancreatitis: expert review. Gastroenterology 2022;163:1107–1114.
69. Vila JJ, Mendioroz FJJ, Yeaton P, et al. EUS is superior to secretin-enhanced cholangio-MRI to establish the etiology of idiopathic acute pancreatitis. Endosc Int Open 2020;8:E1441–E1447.
70. Aisen AM, Sherman S, Jennings SG, et al. Comparison of secretin-stimulated magnetic resonance pancreatography and manometry results in patients with suspected sphincter of oddi dysfunction. Acad Radiol 2008; 15:601–609.
71. Jacob L, Geenen JE, Catalano MF, et al. Prevention of pancreatitis in patients with idiopathic recurrent pancreatitis: a prospective nonblinded randomized study using endoscopic stents. Endoscopy 2001; 33:559–562.
72. Wehrmann T. Long-term results (>/= 10 years) of endoscopic therapy for sphincter of Oddi dysfunction in patients with acute recurrent pancreatitis. Endoscopy 2011;43:202–207.
73. Kaw M, Brodmerkel GJ Jr. ERCP, biliary crystal analysis, and sphincter of Oddi manometry in idiopathic recurrent pancreatitis. Gastrointest Endosc 2002;55:157–162.
74. Das R, Clarke B, Tang G, et al. Endoscopic sphincterotomy (ES) may not alter the natural history of idiopathic recurrent acute pancreatitis (IRAP). Pancreatology 2016; 16:770–777.
75. Cote GA, Durkalski-Mauldin V, Fogel EL, et al. Minor papilla sphincterotomy does not reduce the risk of acute pancreatitis in patients with acute recurrent pancreatitis and pancreas divisum: the sharp trial. Abstract presented at Digestive Disease Week 2025, San Diego, CA May 3–6, 2025.
76. Cote GA, Imperiale TF, Schmidt SE, et al. Similar efficacies of biliary, with or without pancreatic, sphincterotomy in treatment of idiopathic recurrent acute pancreatitis. Gastroenterology 2012;143:1502–1509.e1.

Received November 13, 2025. Accepted January 13, 2026.

Correspondence
Address correspondence to: B. Joseph Elmunzer, MD, MSc, Division of Gastroenterology, Atrium Health-Wake Forest University, 1025 Morehead Medical Drive, Suite 300, Charlotte, North Carolina 28204. e-mail: joe.elmunzer@advocatehealth.org.

Conflicts of interest
The authors disclose no conflicts.

Funding
The Rome Foundation provided organizational and editorial support.