Gallbladder Dysfunction: How Much Longer Will It Be Controversial?

Naeem Goussous^a Gopal C. Kowdley^a Neeraj Sardana^b Ethan Spiegler^c
Steven C. Cunningham^a

Departments of ^aSurgery, ^bGastroenterology and ^cNuclear Medicine, Saint Agnes Hospital, Baltimore, Md., USA

Key Words

Gallbladder dysfunction · Gallbladder dyskinesia ·
Cholecystic dyskinesia · Sphincter of Oddi dysfunction ·
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Abstract

Background: Motility disorders of the biliary tree [biliary dyskinesia, including both gallbladder dysfunction (GBD), and sphincter of Oddi dysfunction] are difficult to diagnose and to treat. **Summary:** There is controversy in the literature in particular regarding the criteria that should be used to select patients for cholecystectomy (CCY) in cases of suspected GBD. The current review covers the history, diagnosis, and treatment of GBD. **Key Messages:** Only >85% of patients with suspected GBD have relief following CCY, a much lower rate than the nearly 100% success rate following CCY for gallstone disease. Unfortunately, the literature is lacking, and there are no universally agreed-upon criteria for selecting which patients to refer for operation, although cholecystokinin (CCK)-enhanced hepatobiliary iminodiacetic acid scan is often used, with emphasis on an abnormally low gallbladder ejection fraction or pain reproduction at CCK administration. There is a clear need for large, well-designed, more definitive, prospective studies to better identify the indications for and efficacy of CCY in cases of GBD.

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Introduction

Biliary dyskinesia (BD) is a controversial group of functional disorders of the biliary system which, according to the Rome III classification [1, 2], is comprised of two disorders, gallbladder dysfunction (GBD) and sphincter of Oddi dysfunction (SOD). The etiology and pathogenesis of these disorders are poorly understood, and diagnostic criteria have been historically controversial. Matters are further complicated by an inconsistent nomenclature, insofar as, for example, GBD has been referred to in the literature as chronic acalculous cholecystitis, gallbladder spasm, and cystic duct syndrome [3, 4], and even more confusingly, as simply BD [5–8]. This latter term, BD, should be reserved for referring to biliary motility disorders in general, viz, to both GBD and SOD, consistent with the Rome III classification. Therefore, for the purposes of this review, the term BD will be avoided unless referring to both biliary motility disorders.

As an indication for cholecystectomy (CCY), GBD is approximately threefold more common in women and has been noted to increase steeply over the past several decades [9–11]. Because, as is widely recognized, the symptoms of SOD and GBD do overlap [2], and both entities should be considered in evaluating a patient thought to have either one or the other disorder, making a distinc-

tion between the two can be challenging for the clinician. SOD is defined as biliary-type pain (as delineated by the Rome III criteria) without other apparent cause and is divided into three types (SOD type I–III) based on the presence or absence of certain laboratory and imaging characteristics [2]. Although patients considered for the diagnosis of SOD are typically those in whom symptoms persist despite previous CCY, some evidence does exist that SOD can occur in patients with an in-situ gallbladder [12]. While the current review will focus on GBD, the clinician should consider SOD in any patient being evaluated for GBD, especially those patients in whom symptoms persist despite CCY. The Rome III diagnostic criteria for GBD and SOD are shown in table 1.

Historical Background

The recognition of biliary pain in the absence of gallstones was first best described in the 1920s. In 1924, Blalock [13] described 139 patients with acalculous cholecystitis out of 735 patients with benign biliary disease. Already in 1926, Whipple [14], in agreement with Blalock's paper, cautioned against CCY 'done with no definite pathology to warrant it.' In his paper 'Surgical criteria for cholecystectomy', he recommended leaving in situ a normal-appearing, acalculous gallbladder, noting that of the 47 patients undergoing CCY with no evidence of gallstones, 76.6% were asymptomatic on follow-up, compared with nearly 90% of calculous cases [14]. Cholecystography was first described in 1924 by Graham and Cole [15]; they used tetrabromophenolphthalein, a substance that is excreted in the biliary tree to allow radiologic imaging of the gallbladder and the biliary tree. The following decade, in a review of 243 patients who underwent CCY in the absence of gallstones, Mackey [16] reported that 30% of patients were completely relieved of symptoms and 30% reported some improvement in symptoms, while 37% were classified as having an unsatisfactory result. Based on the high rate of unsatisfactory results, he too concluded that operation for acalculous gallbladder should be undertaken only for patients with history and operative findings indicative of pathologic changes [16]. Similarly, Glenn and Mannix [17] in 1956 studied outcomes of patients who underwent CCY for acalculous and not acutely inflamed gallbladders, reporting that only 65% of the patients reported improvement in their symptoms and 11% reported some improvement, while 25% reported no improvement. With increasing use of cholecystokinin (CCK) during cholecystography, Freeman et

Table 1. The Rome III criteria for biliary dyskinesia (aka functional gallbladder and sphincter of Oddi disorders)

For both gallbladder dysfunction and sphincter of Oddi dysfunction
Right-upper-quadrant or epigastric pain which is (mandatory criteria)

- 1 Episodic, lasting 30 min or longer
- 2 Recurrent, but generally not daily
- 3 Progressive, building up to a steady level
- 4 Moderate to severe enough to interrupt daily activities
- 5 Not relieved by bowel movements
- 6 Not relieved by postural change
- 7 Not relieved by antacids
- 8 Not explained by other structural disease

The pain may present with one or more of the following (supportive criteria)

- 1 Nausea and vomiting
- 2 Radiation to the back region
- 3 Night-time episodes awakening the patient

For gallbladder dysfunction

Mandatory:

- 1 Criteria for biliary dyskinesia above
- 2 Gallbladder is present
- 3 Normal liver enzymes, conjugated bilirubin, and amylase or lipase

For sphincter of Oddi dysfunction

Mandatory:

- 1 Criteria for biliary dyskinesia above
- 2 Normal amylase/lipase

Supportive:

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

al. [18] in 1975 and others have reported on the use CCK injection to identify patients with acalculous GBD, who may benefit from CCY. In the Freeman study, of 22 patients with either decreased ejection fraction or reproduction of symptoms with injection of CCK, 95% reported relief or improvement of symptoms. Over the ensuing decades since Freeman et al. [18], with improvements in diagnosis, subsequent studies have found similarly high success rates compared with the literature of the early 20th century (table 2).

Pathogenesis

The exact pathogenesis of GBD is unknown, but it is presumed that the pain associated with BD might be related to a functional obstruction of the bile flow out from the gallbladder, due perhaps to a nonoccluding narrow-

Table 2. Studies on GBD

First author and year	n	EF cutoff, %	Mean EF, %	Gallbladder stimulation (CCK dose or fatty meal)	Pain upon stimulation, %	Chronic cholecystitis, %	Cholest-erolosis, %	Stones on final path, %	CCY	Symptom resolution, %	Medical therapy	Symptom resolution, %	Follow-up, months
Veenstra 2014 [71]	34	>35	14	NR	NR	NR	NR	NR	34	88	0	NR	65
Lindholm 2013 [61]	12	>80	88 ^c	NR	NR	100	25	0	12	92	0	NR	16
Wybourn 2013 [8]	126	<45	20 ^a	fatty meal	7	75	NR	0	126	66 (35/53)	0	NR	42
DuCoin 2012 [60]	19	>35	75 ^c	20 ng/kg over 45 min	100	100	0.05	0	19	89	0	NR	22
Carr 2009 [70]	93	<35	18	20 ng/kg 'continuous'	NR	99	NR	0	83	78	10	91	17
Bingener 2004 [11]	60	<35	14	20 ng/kg over 3 min	7	74 (23/31)	3	10	60	75	0	NR	32
Brosseuk 2003 [72]	88	NR	NR	NR	NR	83	2	11	88	93	0	NR	25
Ozden 2003 [73]	48	<35	NR	20 ng/kg over 3 min	NR	72 (26/36)	NR	6 (2/36)	40	68	8	50	NR
Poynter 2002 [3]	26	<35	15	20 ng/kg over 15 min	NR	100	NR	15	26	65	0	NR	30
Chen 2001 [74]	152	<35	18	CCK, NOS	73	NR	NR	NR	152	58	0	NR	15
Yost 1999 [5]	33	<35	15	30 ng/kg	NR	57 (13/23)	NR	NR	27	89	6	67	18
Tabet 1999 [75]	63	<35	18	CCK, NOS	13	68	9	NR	63	47	0	NR	24
Frasinelli 1998 [76]	243	<40	18	20 ng/kg	56	NR	NR	NR	243	95 (171/243)	0	NR	NR
Adams 1998 [65]	50	<35	16	20 ng/kg over 3 min	NR	100	NR	NR	50	78	0	NR	30
Canfield 1998 [69]	218	<50	NR	CCK, NOS	NR	72	24	6	218	71	0	NR	17
Goncalves 1998 [77]	68	<35	15	10 ng/kg over 3 min	NR	95	NR	16	44	80	24	25	33
Mishkind 1997 [78]	42	<35	17	20 ng/kg over 3 min	82 (23/28)	67 (18/27)	11 (3/27)	19 (5/27)	27	96	15	80	>12
Khosla 1997 [79]	35	<35	NR	20 ng/kg over 2 min	NR	83	23	NR	30	67	5	0	9
Jones 1996 [80]	29	<35	9	20 ng/kg over 3 min	45	83	31	17	29	93	0	NR	14
Barron 1995 [81]	38	<35	NR	20 ng/kg over 3 min	NR	95	33	NR	38	100	0	NR	19
Watson 1994 [41]	51	<50	70 ^b	15 ng/kg over 45 min	NR	100	NR	NR	14	93	37	24	3
Sorenson 1993 [82]	11	<35	20	10 ng/kg over 3 min	NR	100	NR	NR	11	100	0	NR	10
Reed 1993 [83]	30	<35	NR	20 ng/kg over 4 min	NR	90	17	7	30	94	0	NR	13
Halverson 1992 [84]	12	<35	NR	20 ng/kg over 3 min	NR	66	25	NR	12	100	0	NR	30
Yap 1991 [36]	21	<40	24	20 ng/kg over 45 min	NR	92	NR	NR	11	91	10	0	32
Misra 1991 [85]	98	<35	NR	20 ng/kg over 3 min	NR	48	NR	7	69	84	29	0	22
Zech 1991 [86]	83	<50	NR	40 ng/kg over 2 min	NR	86 (51/59)	17 (10/59)	8 (5/59)	60	93	23	57	12
Westlake 1990 [66]	26	<35	35 ^b	20 ng/kg over 30 min	NR	27	NR	NR	26	69	0	NR	24
Pickelman 1985 [87]	19	NR	38 ^b	20 ng/kg over 2 min	47	58	NR	5	19	95	0	NR	NR
Fink-Bennett 1985 [35]	14	<35	11	20 ng/kg over 3 min	NR	86	NR	NR	14	100	0	NR	18

NR = Not reported; NOS = not otherwise specified; EF = ejection fraction. ^a Median. ^b Some patients had a normal GBEF. ^c All patients had a normal GBEF.

ing of the cystic duct. However, in a prospective study comparing the presence of crystals within the gallbladder wall between patients with BD and patients undergoing CCY for gallstone disease, Velanovich [19] found no difference in the presence of crystals in the bile or the gallbladder wall between the two groups and the incidence of chronic cholecystitis was similar in both groups.

An abnormality in the smooth muscle layer of the gallbladder causing impaired gallbladder emptying was proposed by Merg et al. [20], who showed a higher incidence of chronic cholecystitis in patients with GBD as compared to normal subjects. Indeed, *in vitro* studies [21] showed that patients with GBD had a higher incidence of absence of spontaneous contractile activity and decreased contractile response to CCK and electrical field stimulation.

GBD has been associated with altered motility in other gastrointestinal organs. For example, impaired gallbladder emptying has been observed more commonly in

adults suffering from slow-transit constipation [22] and achalasia [23], and in children it has been associated with both constipation and gastroparesis [24, 25]. This raises the question of whether functional motility disorders often manifest concomitantly in separate areas of the GI tract. The association in particular between GBD and SOD has been studied by Ruffolo et al. [26], who found significant overlap between these diseases, consistent with other studies [27, 28]. Patients with biliary pain and an acalculous gallbladder were evaluated with sphincter of Oddi manometry, ERCP, and qualitative cholescintigraphy. Of the patients with a gallbladder ejection fraction (GBEF) of <35%, half were found to have associated SOD, and conversely, in patients with SOD, 51% had a depressed GBEF [26]. Given no significant differences in GBEF in patients with normal versus elevated sphincter pressures, the authors concluded that the GBD and SOD may exist independently but can coexist in patients with biliary pain and an acalculous gallbladder. By contrast, in

a recent Hungarian study, Szepes et al. [28] studied 36 patients with symptomatic GBD, 72% of whom (26 patients) were suspected to have associated SOD based on manometry: after endoscopic sphincterotomy in these patients, there was an improvement in the CCK-induced GBEF, transpapillary bile flow and also a significant improvement in symptoms.

Diagnosis

The pain attributed to BD is generally similar in nature to biliary colic caused by gallstones. The diagnostic criteria (table 1) of BD (both GBD and SOD) are pain that: (1) is usually located in the right upper quadrant or epigastric area, (2) is associated with normal liver enzymes, conjugated bilirubin, amylase and lipase, (3) usually lasts for at least 30 min and is recurrent in nature, (4) builds up in a steady fashion and causes pain severe enough to interrupt the patient's activities or to lead the patient to seek medical attention, (5) is not relieved by bowel movement, postural changes or antacids, and (6) cannot be explained by other structural disease [2]. Three additional posttreatment criteria have been proposed to further shore up the diagnosis of GBD: (1) the absence of sludge, stones, or microlithiasis in the gallbladder, (2) decreased GBEF (<40%) on CCK cholescintigraphy, and (3) absence of recurrent symptoms for longer than 12 months [2].

Diagnostic Modalities

CCK Provocation Test

This test found its origins in the work of Ivy and Oldberg [29], who identified the role of CCK in gallbladder contraction in 1928. Its clinical use to evaluate gallbladder function was first reported by Broden [30] in 1958, when he injected CCK during cholecystography to evaluate gallbladder evacuation. This test, however, has fallen out of use, principally due to the subjective, nonquantitative nature of the test, which was found to poorly predict which patients may benefit from CCY [31].

Endoscopic Ultrasound and Endoscopy with Bile Analysis

The use of endoscopic ultrasound (EUS) was proposed for better visualization of the gallbladder to detect stones not visualized by transabdominal ultrasound (TAUS). Thorboll et al. [32] recently used EUS to prospectively study 35 patients with biliary pain and a negative TAUS;

stones were identified in 52.4% of the patients by EUS, and 88% of the patients with a positive EUS had gallstones confirmed on postoperative pathology. After a year of follow-up, 87% of patients with positive gallstones were relieved of symptoms [32].

The microscopic evaluation of bile samples looking for microlithiasis and biliary sludge was also suggested for the evaluation of biliary pain in the setting of a normal TAUS. Dahan et al. [33] compared EUS and microscopic evaluation of bile for detection of microlithiasis and both modalities offered almost equivalent specificity, 86 and 91%, respectively. EUS, however, offered higher sensitivity (96%) compared to the bile examination (67%). Since microscopic evaluation of bile requires the invasiveness of direct cannulation of the common bile duct and because EUS is not available in every center, these modalities are not widely employed in the routine evaluation of acalculous biliary pain. However, every clinician evaluating patients with biliary pain should be aware that microlithiasis, or any cholelithiasis not detected by TAUS may mimic GBD.

Scintigraphy: CCK-Enhanced Hepatobiliary Iminodiacetic Acid Scan

The use of a radioactive bile tracer to quantitatively study gallbladder evacuation was first described by Krishnamurthy et al. [34]. Fink-Bennett et al. [35] combined the use of CCK and nuclear imaging to measure GBEF. In their report, they concluded that given a low GBEF ($\leq 35\%$) and an appropriate clinical and laboratory setting, GBD should be considered. Yap et al. [36] studied GBEF after CCK stimulation in 40 normal volunteers. The mean GBEF of his cohort was 74.5%, and he defined abnormal GBEF as 3 standard deviations below the average (40%). He then prospectively randomized 21 patients with an abnormal GBEF into 2 groups: CCY and no-CCY. On follow-up, 91% of the patients who underwent CCY reported resolution of the symptoms and 9% reported improvement of the symptoms, while none of the patients in the no-CCY group reported symptom improvement. This small trial is the only randomized controlled trial available to date.

The methodology of CCK cholescintigraphy has been subject to variability. Proposing that longer duration of infusion is more physiologic, Ziessman et al. [37] and Ziessman [38] described the infusion of 0.02 $\mu\text{g/kg}$ of Sincalide[®] (synthetically prepared C-terminal octapeptide of CCK) over 30 min in patients fasting for 3–4 h. A multicenter study conducted to investigate the optimal method of infusing CCK concluded that Sincalide infusion

over 60 min offered the least amount of variability in GBEF [39]. Current practice guidelines developed by the Society of Nuclear Medicine Task Force [40], with input from both the American College of Radiology and the European Association of Nuclear Medicine, recommend the infusion of 0.02 µg/kg of Sincalide over a 60-min period with a normal value of at least 38%. However, the effectiveness of this method in chronic gallbladder disease has not been well documented to date. An alternative methodology uses the infusion of 0.015 µg/kg of Sincalide over a 45-min period with GBEF determination at 60 min with a normal value of at least 40% [41].

Other stimulants for gallbladder contractility have been studied as well, especially during shortages of pharmacologic CCK, such as a lactose-free fatty meal [42–46], including the use of a fatty meal during magnetic resonance imaging (MRI) cholangiography to assess GBEF [47]. Indeed, Marciani et al. [48] evaluated a number of food products on gallbladder contractility by studying the changes in gallbladder size with use of MRI, and found that long-chain fatty acids was the most potent stimulator of gallbladder contractility and also induced the highest serum concentration of CCK.

Nonscintigraphic Methods to Assess GBD: TAUS and MRI

TAUS, CT, and MRI have also been used as functional tests in addition to hepatobiliary iminodiacetic acid (HIDA). Irshad et al. [49] have compared HIDA with TAUS to assess gallbladder function and found a reasonably high concordance with a kappa agreement of 0.89. TAUS measurement of gallbladder volume and function, however, is subject to operator variability and results may be inconsistent between institutions [2]. While CT and MRI dynamic cholangiography is largely experimental, it has been shown to correlate with HIDA [50] and has the advantage to detect stones missed on other modalities. Dynamic TAUS is more common in Europe and Asia than the United States, where HIDA remains the gold standard.

The Morphine-Prostigmine Provocation (Nardi) Test

The Nardi test has been used to screen patients with upper abdominal pain for SOD. A positive test is defined by a fourfold rise in serum amylase or lipase along with reproduction of abdominal pain after intramuscular introduction of 10 mg of morphine and 1 mg of prostigmine. Although initial results were promising, subsequent evaluation revealed a lack of specificity precluding widespread use [51].

Treatment

Medical Therapy

Centrally acting antidepressants such as amitriptyline and desipramine have been found to be effective in patients with functional gastrointestinal disorders in general [52], but no studies have proven these medications to be effective in patients with GBD in particular. The antibiotic and motilin agonist erythromycin induces gallbladder contraction and reduces fasting and postprandial gallbladder volumes [53, 54]. This has not translated into routine use of this drug in medical practice, perhaps because of varied effects of erythromycin on the sphincter of Oddi [55]. Overall, no good medical therapy exists [56–58] for GBD.

Cholecystectomy

Multiple studies supporting the use of CCY in the treatment of GBD exist in both the medical [57] and surgical [59] literature. Unfortunately, nearly all are retrospective, with little to no robust, level I data, and controversy persists, as evidenced in the literature, including a recent symposium paper entitled ‘Biliary dyskinesia: does it exist? If so, how do we diagnose it? Is laparoscopic cholecystectomy effective or a sham operation?’ [6] and a review entitled ‘Controversies concerning pathophysiology and management of acalculous biliary-type abdominal pain’ [58]. Further muddying the GBD waters, studies describing normokinetic [60] and hyperkinetic [61] gallbladders causing GBD, treated with CCY, have been recently published (table 2).

Therapeutic response to CCY, i.e. either partial or complete symptom resolution, in the literature has been reported to range anywhere from 38 to >90% [58]. In their prospective randomized trial, Yap et al. [36] reported symptom resolution in 91% of patients who underwent CCY as compared to no change in symptoms in patients who were managed without CCY. In a meta-analysis examining the effectiveness of CCY, Ponsky et al. [7] concluded that 98% of patients reported complete or partial symptom relief after CCY. A Cochrane review article was published in 2009 [62] to study the efficacy of CCY for BD, but the authors were able to include only one study, the prospective study conducted by Yap et al. [36], and concluded that the level of evidence is not sufficient to recommend CCY for patients with GBD and that further randomized clinical trials are needed. Table 2 compares studies evaluating the effect of CCY on the symptoms of GBD.

Factors Associated with Symptom Relief after CCY

A meta-analysis of 9 articles looking at the ability of GBEF to predict relief of symptoms following CCY showed that a high proportion of patients with symptoms typical of GBD had relief following CCY, regardless of the GBEF: 94% of patients with a reduced GBEF and 85% with normal GBEF; $p = 0.56$), leading the authors to conclude that data supporting the use of GBEF in the evaluation of patients with abdominal pain suggestive of biliary disease are insufficient, with the caveat that the quality of the data was low [63]. Similarly, others have found favorable outcomes after CCY even in patients with normal GBEF [3, 8, 60, 61, 64–66]. For instance, Wybourn et al. [8] retrospectively followed 126 patients with GBD treated with laparoscopic CCY. The authors reported that 78% of patients reported relief of pain in the perioperative period irrespective of the GBEF, but did note that obese patients were more likely to have persistent pain in the perioperative period. Similarly, a recent meta-analysis found no benefit in preventing BD (or other biliary pathology) of incidental CCY at time of gastric bypass for morbid obesity [67].

Although reproduction of the biliary pain at the time of CCK injection during the HIDA scan has been considered predictive, data are scant, with very few studies reporting reproduction of pain during HIDA. By contrast, Morris-Stiff et al. [68], studying 42 patients who underwent CCY based on symptom reproduction at CCK injection (17 with GBEF <35%, and 25 with normal GBEF), found that 100% of the patients with reproduction of symptoms upon CCK injection had relief of the biliary symptoms following CCY; no patients without symptom reproduction were included in the study. Another study, by Canfield et al. [69], did include patients both with and without reproduction of symptoms on CCK injection and both with and without abnormal (<50%) GBEF. Among

patients with abnormally low GBEF, symptom resolution was more common in patients whose symptoms were reproduced at CCK injection versus those without reproduction of pain upon CCK injection >70 and <60%, respectively. A prospective nonrandomized cohort study published in 2009 [70] suggested that pain upon CCK injection predicted success following CCY, but few details are provided. And as described above, DuCoin et al. [60] studied a small group ($n = 19$) of patients, all of whom met the Rome III criteria for GBD, had normal GBEF, and had pain reproduced upon injection of CCK, with a complete pain resolution rate of 90% and an improvement rate of 95%.

Given the low quality and quantity of data regarding predicting which patients with GBD will benefit from CCY, more prospective studies are necessary. With adequate data, the relatively low success rate in treating GBD with CCY may approach the nearly 100% success rate associated with treating symptomatic cholelithiasis with CCY.

Conclusion

GBD should be considered in patients presenting with recurrent right-upper-quadrant abdominal pain in the absence of visualized gallstones on abdominal ultrasound, meeting the Rome III criteria. Based on poor-quality data, it appears that CCY may offer partial or complete symptomatic relief in more than 85% of patients. Because of the overlap in symptoms, patients with persistent symptoms after CCY should be evaluated for SOD. There is a need for a large, well-designed, adequately powered, prospective studies to better examine and clarify the indications for and efficacy of CCY in the currently controversial GBD.

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