

Primary Recurrent Common Bile Duct Stones: Timing of Surgical Intervention

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Abstract

Cholelithiasis (gallstones) is a very common medical problem worldwide, with 5-30% of patients demonstrating a combined condition of cholelithiasis and choledocholithiasis (common bile duct stones (CBDS)). CBDS are usually classified as primary or secondary stones. Primary CBDS are defined as stones detected 2 years or more following cholecystectomy, while secondary stones, the most common type, usually migrate from the gallbladder to the bile ducts. Recurrent CBDS are defined as stones detected 6 months or more following endoscopic retrograde cholangiopancreatography (ERCP) with complete duct clearance. Although ERCP with endoscopic sphincterotomy has emerged as the main therapeutic option for CBDS, with up to 95% bile duct clearance rate, up to 25% of said patients develop recurrent bile duct stones. Thus far, several issues related to recurrent CBDS are still unclear and questions regarding this specific pathology have no precise answers: how many trials of ERCP and endoscopic sphincterotomy should be attempted before referring the patient for surgical management? Is there an association between risk factors and early surgical intervention? Thus, currently, there is no worldwide scientific-based consensus regarding the best management of this specific group of patients. The main issue for this article is to review the relevant English literature and find out the main high risk factors for recurrent CBDS, and form a diagnostic and treatment plan, hence, identifying the subgroup of patients that will benefit from early surgical management, preventing further ERCP-associated complications.

Keywords: Recurrent CBDS; ERCP; Endoscopic sphincterotomy; Risk factors; Surgical intervention

Introduction

Gallstone disease (cholelithiasis) is a very common medical

problem worldwide, especially in developed countries [1, 2]. A significant difference of cholelithiasis by ethnicity/race is noted, with Hispanic people of Central and North America having the highest prevalence rate [3]. Although most of these patients remain asymptomatic throughout their lifetimes, 10-25% suffer various gastrointestinal symptoms and develop complications [4-6]. Five to thirty percent of patients have combined cholelithiasis and choledocholithiasis (common bile duct stones (CBDS)) at the time of diagnosis [7]. CBDS are usually classified as primary, when detected 2 years or more following cholecystectomy, or as secondary, originating from the gallbladder, when detected up to 2 years following cholecystectomy. Recurrent CBDS are defined as stones found 6 months or more following initial endoscopic retrograde cholangiopancreatography (ERCP) with complete duct clearance [8, 9].

While cholesterol stones are the most common gallstones (75-80%), recurrent CBDS are usually pigment stones, mainly brown stones, associated with recurrent biliary infections [10, 11]. The hypothesis behind this association is that, following ERCP and endoscopic sphincterotomy, a laxity of the sphincter of Oddi develops, and this in turn causes backward flow of duodenal contents into the biliary and pancreatic ducts, and thus, recurrent infections with stone formation.

Recurrent CBDS could be asymptomatic, found incidentally by radiological tests made for non-relevant disease, or it could be symptomatic, presenting as obstructive jaundice, acute suppurative ascending cholangitis, pancreatitis, etc. [11].

Since its introduction in 1974, initially as a procedure of choice for elderly unfit patients for surgical management of CBDS, ERCP with endoscopic sphincterotomy has become the procedure of choice for the treatment of CBDS in all category of patients worldwide [12]. Although the procedure is usually considered safe and effective, it is not an innocuous one and complications (4-16%), either early or late, may develop. Early complications include post-ERCP pancreatitis (the most common - up to 6%), hemorrhage, cholangitis and perforation (the least common reported in 0.08-1% of cases) [13-15]. Late complications include papillary stenosis or recurrent CBDS, with the latter growing into a burden for both the patients and the healthcare systems.

Although ERCP along with endoscopic sphincterotomy is considered the first-line therapeutic modality for CBDS, several issues related to recurrent CBDS are still unclear and questions regarding this specific pathology have no clearcut answers: how many trials of ERCP and endoscopic sphinc-

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terotomy should be attempted before referring the patient for surgical management? Following which episode of symptomatic recurrent CBDS the patient should be operated on? And is there an association between risk factors and early surgical intervention?

The absence of answers for the aforementioned questions is the main reason for the absence of worldwide scientific-based therapeutic consensus regarding primary recurrent CBDS.

This review article is to find out the possible independent risk factors for primary recurrent CBDS and further determine its potential association with surgical intervention.

Risk Factors for Recurrent CBDS

Stones of the gallbladder and bile duct are usually classified into three major types: cholesterol stones, pigment stones and mixed stones [16, 17]. Cholesterol stones are the major type (75-80%) usually containing more than 50% cholesterol. Risk factors for cholesterol stone formation include hyperlipidemia, female gender, total parenteral nutrition and others. Pigment stones include black stones, associated with hemolysis and liver cirrhosis, and brown stones (the most common type of CBDS) which are associated with recurrent bile duct infection [10, 11, 18]. Pigmented stones, mainly the brown type, are the most common type of primary recurrent CBDS.

In addition to recurrent bile duct infection, specifically following ERCP and endoscopic sphincterotomy, other risk factors for recurrent CBDS were reported: patient's age, patient's gender, genetic mutations, stone's number and size, stone location along the common bile duct (CBD), diameter of the bile ducts, the presence of duodenal diverticulum, previous ERCP with endoscopic sphincterotomy, metabolic factors, drugs and others.

Age

Age older than 65 years old is considered a very high independent risk factor for CBDS recurrence. In his study, Fritz et al [19] reported a recurrence rate of up to 30% following ERCP and endoscopic sphincterotomy in patients older than 65 years. Moreover, 86.4% of the CBDS recurrences were reported in the elderly group of patients (older than 65 years old) [20]. These findings were also demonstrated by Deng et al [7], when he concluded that age above 65 years old is regarded as an independent risk factor for CBDS recurrence following ERCP and endoscopic sphincterotomy.

Gender

Due to the high estrogen levels, it is well known that female patients are more susceptible to develop choledocholithiasis. On the other hand, as have been already reported by several studies [21, 22], there is no correlation between gender and risk of CBDS recurrence.

Genetic mutations

Several genetic mutations have been examined for gallbladder and bile duct stones formation, of which the *ABCB4* mutation (encoding the hepatobiliary flippase) is the main genetic risk factor for stones recurrence [23]. The aforementioned genetic mutation leads to a defect in the multidrug resistance protein 3 (MDR3), which in turn causes phosphatidylcholine levels reduction, increasing the risk for stones formation.

The number and diameter of the CBDS

The number and diameter of stones present in the bile ducts have been the subject of controversy in the literature. The main hypothesis suggests that as the diameter and number of the stones is higher, the risk for CBDS recurrence is higher [7, 22]. Several theories can explain this, including loss of bile duct peristalsis due to dilation of the bile duct as a result of large stones, bacterial overgrowth and bile duct infection (which can predispose patients to pigment stone development) and more difficult endoscopic procedures, with higher probability for lithotripsy usage and higher failure rates.

In the study by Deng et al [7], a stone diameter of 10 mm or more was an independent risk factor for stone recurrence. The findings of Deng et al were also demonstrated in another study [22], where the recurrence rates at 5, 10 and 15 years were higher when stone diameter was 11 mm or more. These findings were contradicted by several studies that concluded there is no correlation between stone size and risk of CBDS recurrence [24, 25].

Several studies demonstrated that multiple bile duct stones (two or more) is a risk factor for CBDS recurrence with proven statistical significance [26, 27]. Although patients with multiple bile duct stones had a higher rate of recurrence, it was not significant statistically in relation to the control group in the study by Deng et al [7]. Larger number and size of stones could be a risk for residual bile duct stones rather than risk for recurrence as reported by Cheon and Lehman [24], and thus, the outcomes are related more to management methods than patient factors.

Stone position

Stone position along the CBD was mentioned as a possible risk factor for recurrence. It was suggested that as the stone is more distally located and close to the sphincter of Oddi, the greater the pressure it causes with massive damage [28]. Up till now, there is no currently published study regarding this issue, and future studies are encouraged to investigate this suggestion.

CBD diameter

The diameter of the CBD as a risk factor for CBDS recurrence was examined extensively during the last two decades and most studies report a strong correlation. The hypothesis behind this correlation is that dilation of the bile duct causes

functional impairment of bile duct peristalsis, which in turn leads to stasis, bacterial infection and stone formation [29]. In his study, Pereira-Lima et al [30] showed that the risk for CBDS recurrence was four-folds higher in patients with CBD diameter of 15 mm or higher than in patients with CBD diameter of 10 mm or less. The risk of CBDS recurrence was 46% in patients with CBD diameter of more than 15 mm compared to only 20% in patients with CBD diameter of less than 12 mm [31]. A common bile duct of more than 15 mm was also a strong risk factor for CBDS recurrence with statistical significance in the study by Li et al [27]. The finding of strong correlation between CBD diameter and CBDS recurrence was also demonstrated in several other studies [7, 26, 32, 33]. Although the diameter of the CBD is already a confirmed strong risk factor for CBDS recurrence, the precise diameter is yet to be known, as different diameters had shown different recurrence rates. A consensus is that a CBD diameter of 15 mm or more is a high risk factor for recurrent CBDS.

Periampullary diverticulum

The presence of duodenal periampullary diverticulum had also been reported as a risk factor for CBDS recurrence. Duodenal diverticulum, firstly recognized in 1710 by Chomel, is uncommon with an incidence rate of 15-22% by post mortem studies [34, 35]. Periampullary diverticula is the most common type of duodenal diverticulum, usually located within 2 - 3 cm from the papilla of Vater [36]. Three different types of periampullary diverticulum are known, depending on the location of the major papilla: type A - inside the diverticulum, type B - adjacent to the diverticulum and type C - outside the diverticulum. Although the precise mechanism is yet to be known, it is already proved that periampullary diverticulum is a strong predisposing factor for stone formation as well as stone recurrence [37, 38]. The most accepted mechanism according to manometric studies is that the presence of periampullary diverticulum leads to decreased pressure in the sphincter of Oddi, which in turn leads to backflow of intestinal flora to the bile duct and the formation of pigment stones. The reported incidence of bile duct stones (mainly pigment stones) in patients with periampullary diverticulum is almost 89% [39].

ERCP

Although ERCP, especially when accompanied by endoscopic sphincterotomy, is the main therapeutic option for CBDS, it is regarded as a risk factor for CBDS recurrence. Following endoscopic sphincterotomy, stricture of the papilla may develop, in addition of bile duct dilation and infection. These in turn may cause CBDS recurrence. In his study which included 11 centers, Yasuda et al [40] demonstrate that ERCP with endoscopic sphincterotomy is an independent risk factor for CBDS recurrence. CBDS recurrence can develop following either ERCP with endoscopic sphincterotomy, balloon dilatation or stent insertion. The risk of recurrence was less after balloon dilatation (8.5%) than endoscopic sphincterotomy (15%) on follow-up

period of more than 90 months [41]. Similar findings were also reported in the study by Kojima et al [42]. Following balloon dilatation, the function of the sphincter of Oddi was preserved in 70% of patients. ERCP with either endoscopic sphincterotomy, balloon dilatation or stent insertion was regarded as an independent risk factor for CBDS recurrence [7, 22], with endoscopic sphincterotomy patients having the higher rates of recurrences. Biliary stent insertion is considered an alternative option mainly for unstable patients, due to severe ascending cholangitis, and for elderly patients. Interesting findings were reported by Choi et al [43]; in his study which included 483 patients, Choi et al showed that patients who have had stent insertions to the bile duct for a short period had less risk for recurrent CBDS. On the other hand, stent insertion for a long time was an independent risk factor for CBDS recurrence [44].

Other factors

Metabolic related risk factors for gallbladder and bile duct stones are diverse and include: obesity, hyperlipidemia, insulin resistance diabetes mellitus, fatty liver, hypercalcemia and hyperuricemia [45]. Although there is no study investigating the correlation between these factors and primary CBDS recurrence, it is believed that these should be regarded as risk factors for recurrence.

Of the several drugs investigated, proton pump inhibitors (PPIs) were found to increase the risk for CBDS recurrence, especially following ERCP and endoscopic sphincterotomy [46]. PPIs cause duodenal flora changes with bacterial overgrowth and recurrent ascending cholangitis.

Surgical Intervention

Surgical managements of CBDS have decreased dramatically since the introduction of ERCP as the main therapeutic procedure [12]. Nowadays, the role and timing of surgical intervention, especially for recurrent CBDS, is unknown due to lack of studies (mainly prospective) that compare it with other therapeutic procedures. It is usually indicated in very special cases as failure or unavailability of endoscopic management and other procedures such as percutaneous transhepatic biliary drainage (PTBD). Surgical procedures usually include CBD exploration, either by open or minimally invasive (laparoscopy) techniques, along with choledochoscopy, intra-operative cholangiogram, stone extraction with T-tube insertion, choledocho-duodenostomy/jejunostomy or resection of CBD with Roux-en-Y gastrointestinal reconstruction [47]. Due to technological advancement, laparoscopic bile duct exploration has become very safe and cost-effective [48, 49]. Stone clearance rate is up to 95% following laparoscopic CBD exploration, with morbidity and mortality rates of 4-16% and 0-2%, respectively [50, 51]. In the study by Tai et al [52], stone clearance rate was 100%, with 0% recurrence rate on a median follow-up of 16 months. Patients treated by this approach have a shorter hospital stay and lower hospital costs than patients treated by ERCP and endoscopic sphincterotomy [49]. Variable litho-

Table 1. Level of Risk for the Relevant Risk Factors for Recurrent CBDS

Level of risk	Risk factors
High risk	Age older than 65 years old; Genetic mutations (<i>ABCB4</i> gene mutation); Dilated CBD (more than 15 mm); Periapillary duodenal diverticulum; Previous ERCP with endoscopic sphincterotomy
Intermediate risk	Stone diameter (more than 1 cm); Multiple stones (more than 1); ERCP with balloon dilation; ERCP with stent insertion
Low risk	Female gender; Metabolic-related factors; Drugs (PPIs)

Metabolic-related factors: obesity, hyperlipidemia, hypercalcemia, hyperuricemia, insulin resistance diabetes mellitus and fatty liver. CBDS: common bile duct stone; ERCP: endoscopic retrograde cholangiopancreatography; PPIs: proton pump inhibitors.

tripsy maneuvers, such as laser, electrohydraulic and extracorporeal shockwave, have been described with different results. These therapeutic options are barely used nowadays due to its high risk of bile duct wall damage and bleeding [53].

CBD exploration by an open approach is another accepted surgical therapeutic option, with high clearance rates of bile duct stones. In his meta-analysis, Martin et al [54] demonstrated higher rates of successful stone clearance than ERCP, with no morbidity and mortality difference. On the other hand, bile duct stone clearance rates were identical for laparoscopic bile duct exploration and ERCP, with identical morbidity and mortality rates. In another study, the recurrence rate for primary CBDS following ERCP with endoscopic sphincterotomy was higher (46%) than for open surgical exploration of the bile ducts with lithotripsy alone (29%) and open surgical bile duct exploration with lithotripsy and choledochojunostomy (3%) [55]. There was no significant difference in complication rates for the previously mentioned therapeutic options.

Open surgical exploration of the bile ducts can be approached either by choledocho-enterostomy, stone extraction with T-tube insertion or by sphincterotomy [56]. Choledocho-enterostomy is the preferred option in the presence of multiple stones and when bile ducts are dilated more than 2 cm. This can be contemplated by resection of the bile ducts with Roux-en-Y choledochojunostomy or with choledocho-duodenostomy without resection. One of the main complications of the latter procedure is “sump syndrome”, which develops in 1% of patients, when food or debris stagnates in the distal part of the CBD distal to the anastomosis [56].

Both surgical options, the laparoscopic and the open approach, are an accepted surgical procedure and depend mainly on the surgeon’s experience, which should dictate which option to perform.

Discussion

Since its introduction during the early 1970s, ERCP with endoscopic sphincterotomy has gained a worldwide acceptance as the main therapeutic option for CBDS. Although this non-surgical procedure is regarded as safe and highly successful, complications, either early or late, mild or severe, may develop. Of the late complications, recurrent primary CBDS is well known, and has emerged as a main topic of investigation during the last two decades due to its heavy burden on health institutions. Recurrent primary CBDS could be asymptomatic and discovered incidentally, or symptomatic with variable

presentations, such as obstructive jaundice, ascending suppurative cholangitis or biliary pancreatitis.

Although risk factors for recurrent primary CBDS have been studied in a very thorough manner by previous already published retrospective studies and review articles, no manuscript discussed the correlation between these risk factors and therapeutic strategies to be followed by the treating physicians. Hence, the number of ERCP trials to be performed for the management of recurrent primary CBDS is unknown, making treatment of this unique group of patients physician-based and not scientific-based.

As mentioned before, several risk factors have strong association with CBDS recurrence with statistical significance. These factors, which include age older than 65 years old, specific genetic mutations (mainly *ABCB4* mutation), dilated CBD (more than 15 mm), periampullary duodenal diverticulum and previous ERCP with endoscopic sphincterotomy should be regarded as high risk factors for stones recurrence (Table 1).

Literature controversy exists for other reported risk factors, mainly stone diameter and number and ERCP with balloon dilatation or stent insertion. As have been mentioned earlier, variable outcomes in terms of level of risk have been shown and failure of these factors to meet statistical significance in all published articles. Therefore, multiple CBDS (more than one), large diameter of the stone (more than 1 cm) and ERCP with balloon dilatation or stent insertion may be regarded as intermediate risk factors for recurrent primary CBDS.

In the absence of scientific evidence for a strict correlation, known risk factors for stone formation such as metabolic related factors, female gender, drugs (mainly PPI) and stone position along the biliary tree, may be regarded as a low risk for recurrence.

Nowadays, it is well known that the risk for recurrence of CBDS is directly proportional to the number of recurrences. As the number increases, the risk increases as well. In his study which included 46,181 patients, Park et al [57] showed first, second and third recurrence rates of 11.3%, 23.4% and 33.4%, respectively on a median follow-up of 4.2 years. High rates of 19.5% for second recurrence and 44% for third recurrence were also reported [6]. Recurrent endoscopic intervention may cause recurrent sphincter of Oddi and bile duct epithelial injury, leading to inflammation, necrosis, scar formation and stenosis. This in turn will increase the risk for CBDS recurrence.

Due to the aforementioned histological changes and risk for bile duct stenosis and CBDS recurrence, patients with recurrent primary CBDS should be managed by a multidisciplinary team of physicians consisting of hepatobiliary surgeons,

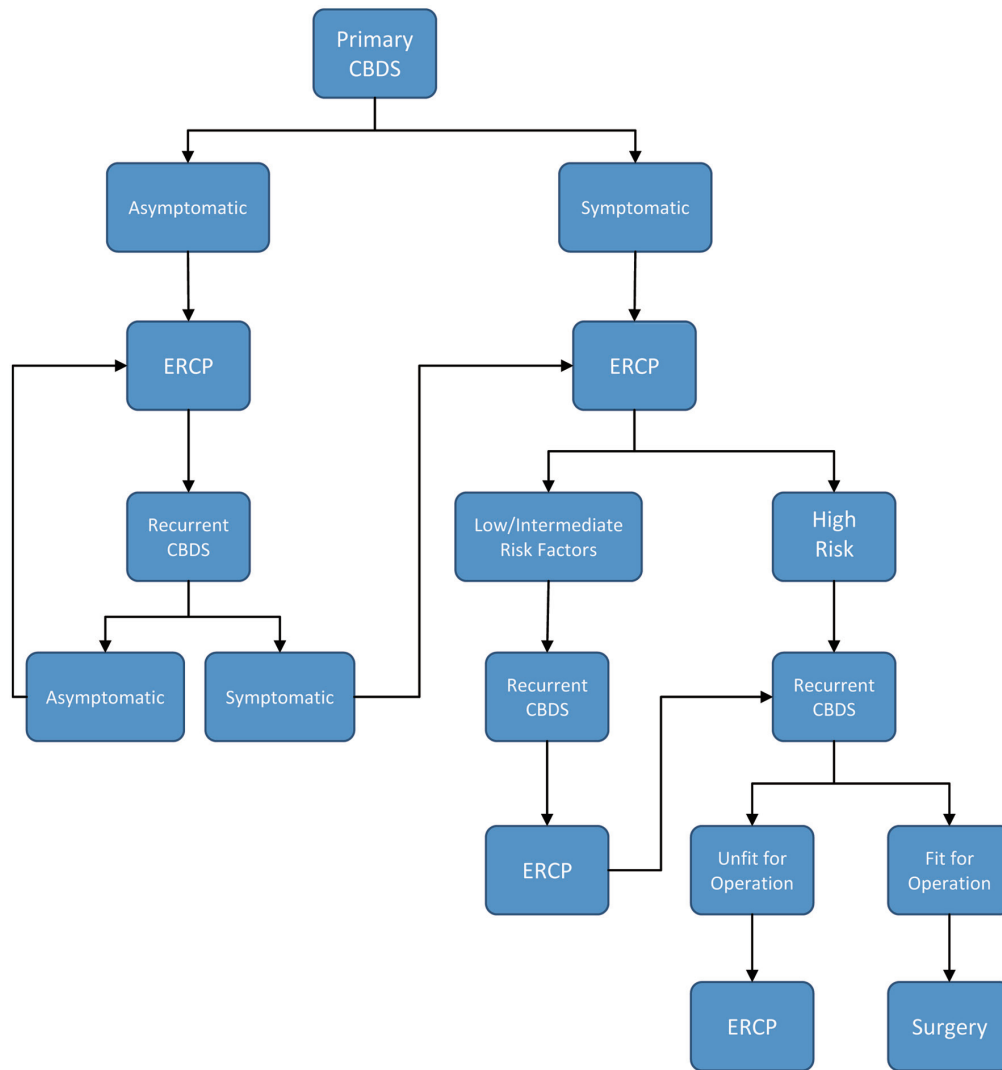


Figure 1. A suggested flow chart for the management of recurrent primary CBDS according to risk factors. CBDS: common bile duct stone.

interventional gastroenterologists and abdominal radiologists.

A suggested therapeutic flow chart is shown in Figure 1.

Primary recurrent CBDS may be classified into two major groups: asymptomatic and symptomatic. ERCP should be the initial therapeutic procedure for both. Of the symptomatic group, patients with one or more high risk factors should be identified during the first episode and labelled as high risk group for recurrence. This group should be considered for early surgical management, if a second symptomatic episode occurs and the patient is fit for surgical intervention. Patients who are at high risk for operation should be scheduled for repeated ERCP. Symptomatic patients with intermediate or low risk factors should be treated by a repeated ERCP if a second episode develops, and planned for surgical intervention if a third symptomatic episode occurs. Following initial management by ERCP for asymptomatic patients, a repeated ERCP should follow if patients develop recurrence accompanied by symptoms. If future recurrences develop, continuation of man-

agement will be identical to the symptomatic group.

Conclusion

Primary recurrent CBDS are uncommon, yet a known late complication of ERCP procedures and pose a heavy burden on health systems. Risk factors are well known, but their effect on therapeutic decisions has never been tested. In the absence of therapeutic consensus, a multidisciplinary team management approach is highly recommended, and patients with high risk factors should be identified and referred for early surgical intervention if a second symptomatic episode develops.

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Conflict of Interest

None to declare.

Author Contributions

SM collected and analyzed the data. SK contributed to writing the manuscript. The paper was drafted by SM and SK. Critical revisions and final approval were made by YK and SK.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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