

Step-by-step strategy in the management of residual hepatolithiasis using post-operative cholangioscopy

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Abstract: Hepatolithiasis is the presence of calculi within the intrahepatic bile duct specifically located proximal to the confluence of the left and right hepatic ducts. The ultimate goal of hepatolithiasis treatment is the complete removal of the stone, the correction of the associated strictures and the prevention of recurrent cholangitis. Although hepatectomy could effectively achieve the above goals, it can be restricted by the risk of insufficient residual liver volume, and has a 15.6% rate of residual hepatolithiasis. With improvements in minimally invasive surgery, post-operative cholangioscopy (POC), provides an additional option for hepatolithiasis treatment with higher clearance rate and fewer severe complications. POC is very safe, and can be performed repeatedly until full patient benefit is achieved. During POC three main steps are accomplished: first, the analysis of the residual hepatolithiasis distribution indirectly by imaging methods or directly endoscopic observation; second, the establishment of the surgical pathway to relieve the strictures; and third, the removal of the stone by a combination of different techniques such as simple basket extraction, mechanical fragmentation, electrohydraulic lithotripsy or laser lithotripsy, among others. In summary, a step-by-step strategy of POC should be put forward to standardize the procedures, especially when dealing with complicated residual hepatolithiasis. This review briefly summarizes the classification, management and complications of hepatolithiasis during the POC process.

Keywords: bile duct stricture, calculi removal, post-operative cholangioscopy, residual hepatolithiasis, step-by-step strategy

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Introduction

Hepatolithiasis, defined as intrahepatic duct calculi, is a benign bile disease with a challenging treatment and high recurrence.¹ The prevalence of hepatolithiasis is persistently high, especially in East Asian countries, including China, Korea, Malaysia and Indonesia.^{2,3} Bile stasis, repeated infection and biliary ascariasis are considered important risk factors.⁴ Hepatolithiasis may be complicated by biliary strictures, liver abscess, liver cirrhosis and cholangiocarcinoma.⁵ Although the current understanding of the disease has increased globally, there is still an urgent need for treatments in both the East and West.⁶

In general, the ultimate goal of treating hepatolithiasis is the clearance of calculi, the correction of strictures, the removal of lesions and the restoration of bile drainage.⁷ The most efficient treatment for patients with hepatolithiasis remains unclear. With improved medical technology, it has been reported that various therapeutic measures are available for the management of hepatolithiasis, including surgical treatments, endoscopic approaches, liver transplantation, chemical bile duct embolization (CBDE) and a combination of these.^{8–10} Generally, hepatectomy seems to be the optimal treatment, reducing the risk of recurrent intrahepatic calculi and cholangitis by removing the calculi and lesions simultaneously.¹¹ However,

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hepatectomy is applied primarily for patients with calculi distributed on one side of the diseased hepatic lobe or segment with atrophy, fibrosis or cirrhosis, and it is not suitable when intrahepatic biliary calculi are present in both hepatic lobes.¹² It also goes against the ideal of maximum retention of normal liver tissue. Owing to these limitations, the reported complete clearance is low and the incidence of residual bile duct calculi in patients is still high.¹³

In recent years, new endoscopic procedures, such as post-operative cholangioscopy (POC), percutaneous transhepatic cholangioscopy (PTCS), endoscopic retrograde cholangiopancreatography (ERCP) and direct peroral cholangioscopy have been proven efficient in the treatment of residual hepatolithiasis with/without surgery.¹⁴ POC provides an attractive option for complicated indications. The procedures of POC have been shown to be simple and safe, and result in fewer complications, especially in the treatment of recurrent/peripheral calculi and indeterminate strictures.^{15,16} At our hepatolithiasis treatment centre in China, we successfully treat >3000 POC cases each year. In this review, we aim to briefly summarize the POC-related techniques used in the management of residual hepatolithiasis.

Classification of hepatolithiasis

Hepatolithiasis has been classified based on origin, biochemical structure and clinical indication, among others. Based on origin, hepatolithiasis can be classified into two types: primary, referring to those calculi formed *de novo* in intrahepatic ducts; and secondary, referring to those originating in either the gallbladder or the common bile duct, which then migrate to the intrahepatic ducts.¹ As a biochemical classification, hepatolithiasis is divided into calcium bilirubinate calculi, cholesterol calculi and mixed calculi.¹⁷ Cheon and colleagues classified hepatolithiasis according to location into three types (unilateral, bilateral or multiple) regarding calculi and lobe stenosis.¹⁸ Tsunoda and colleagues divided calculi into four types based on stone location and the presence or absence of stenotic lesions and/or localized dilatation of the intrahepatic bile ducts.¹⁹ 'Dong's Classification' is designated to determine reasonable approaches for treating hepatolithiasis.²⁰ Hepatolithiasis is classified into two types. Type I is a localized calculus disease. Type II is a diffuse calculus disease, which is divided into

three subtypes with various degrees of hepatic pathological complications. An additional type of hepatolithiasis with extrahepatic stones is represented by the letter E, which also represents the function of the sphincter of Oddi. This type can be divided into three subtypes: Ea, Eb and Ec. Although there are no universal criteria for the classification of hepatolithiasis, we suggest it should be based on the pathological characteristics of the bile duct and hepatic parenchyma in order to help in the determination of the best treatment option.

Management of hepatolithiasis

A reasonable treatment is required to resolve long-standing cholangitis, reduce the recurrence of hepatolithiasis and avoid the later development of cholangiocarcinoma.²¹ Surgical procedures are considered to be preponderant in the treatment of unilateral hepatolithiasis with atrophy or fibrosis.²² When combined with other improved supplementary measures, it could be more precise and efficacious than hepatectomy. Three-dimensional visualization technology has guided hepatic segment resection, achieving accurate pre-operative diagnosis and higher complete stone clearance rates.²³ Robotic liver resection reduces blood loss and shortens hospital stays compared with the traditional open approach.²⁴ However, the complexity and variability of the hepatic anatomy in complicated hepatolithiasis increases surgery-related complications.^{13,18}

Although intra-operative cholangioscopy promotes the rate of clearance, it is impossible to attain full calculi clearance during the operation because of the limited resection range during hepatectomy and the long periods of anaesthesia.²⁵ Patients with poor general condition are not able to withstand the surgery. Therefore, endoscopy causes less injury in the treatment of hepatolithiasis in cases of high surgical risk and previous biliary operations.²⁶ Intra-/post-operative POC is associated with reductions in the rates of residual stones and re-operation.²⁵ PTCS is a reasonable alternative or supplementary therapy for hepatolithiasis when a partial hepatectomy is not indicated, especially with dilated bile ducts.²⁷ ERCP and peroral cholangioscopy have played an important role in common bile duct (CBD) stones; in a similar manner the traditional mother-daughter system has helped to non-invasively diagnose and manage stones within the bile duct

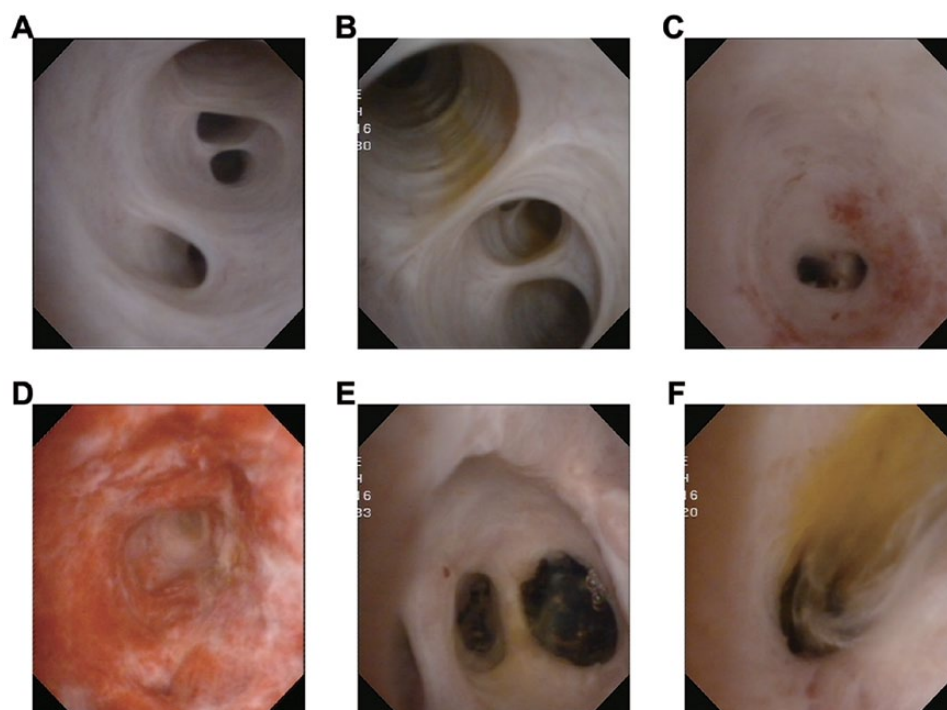


Figure 1. Endoscopic examination of intrahepatic bile ducts. Normal bile ducts (a), dilatated bile ducts (b) and strictured bile ducts (c) were seen under cholangioscopy. Inflammatory mucosa (d) was often shown after removal of calculi due to cholangitis. Two types of complicated calculi were present, including obvious impacted stones (e) and hidden stones in the form of a comet tail sign (f).

tree.^{28,29} In terminal hepatolithiasis there is severe liver failure, for which a healthy donor liver is required.²⁰ Though surgical techniques and peri-operative management could fully meet the needs of liver transplantation, only 27 successful cases have been reported in four centres since 2002.³⁰ CBDE has been experimentally proved to be a potentially effective therapeutic approach for treating and preventing the recurrence of hepatolithiasis.³¹ It is rarely used in clinical practice, except for two cases reported in 2008.³²

History and procedure of POC in treating hepatolithiasis

In the 1940s, cholangioscopy was first introduced; its use was popularized in the following decades.³³ Direct endoscopic view of the biliary tree first occurred when an endoscopist examined a patient with choledochoduodenostomy.³⁴ Since then, cholangioscopy was utilized for patients with calculi located within the intrahepatic bile ducts.³⁵

POC has been reported to be a safe and simple procedure that is useful in the treatment of

intrahepatic stones.³⁶ As a minimally invasive technique, cholangioscopy gradually evolved from the rigid to the soft, and from fibre-optic scope to electronic scope.^{18,28} It has a higher rate of biliary calculi removal and lower rate of recurrence and complications.^{15,37,38} POC is well-suited for patients without full clearance of calculi during surgery,³⁹ and the general procedure is as follows. After the cholangioscope (CHF-V, Olympus, Japan; ECN-1530, PENTAX, Tokyo, Japan) is introduced into bile ducts through the sinus, the examination of CBD and intrahepatic bile ducts is conducted to differentiate the normal, dilatated and strictured lumens (Figure 1(a–c)), to confirm the mucosal condition of the stem and branch tracks (Figure 1(a) and (d)), and to evaluate the distribution, quantity, size and characters of calculi (Figure 1(e)). A comet tail sign often indicates impacted stones (Figure 1(f)). Then, hepatolithiasis is managed by repeated irrigation, basket extraction, lithotripsy and so on through the accessory sinus of the cholangioscope. The reported success rate of POC for residual stone removal ranges from 60 to 90% for intrahepatic duct

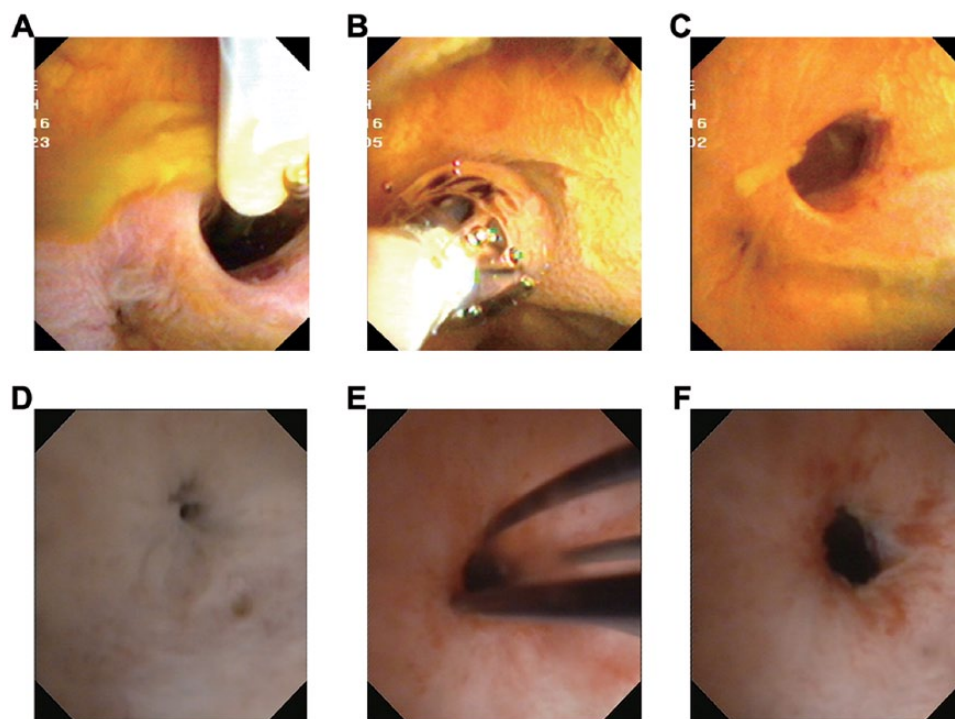


Figure 2. Strictures dilatation in intrahepatic bile ducts. In general, two methods are most widely used to relieve strictures. The first is balloon-based dilatation (a–c); the other strategy is basket-based dilatation (d–f).

calculi.^{40,41} Kong and colleagues reported 2882 POC sessions performed on 986 patients with residual bile duct stones from 1980 to 2008, resulting in no mortalities, 28 failures, 13 complications and 95.5% clearance of cases.²⁵

Complicated calculi management by POC

The management of hepatolithiasis is based upon complete removal of calculi, elimination of biliary strictures and reduction of calculus recurrence. In spite of advances in cholangioscopy, problems such as intrahepatic strictures, the presence of large and impacted calculi and unreached peripheral calculi are the major obstacles to success.

Biliary strictures

Hepatolithiasis usually has a high frequency of associated tract strictures, which is a major cause of treatment failure and is also the main cause of calculi recurrence.^{42–44} Strictures are usually caused by recurrent cholangitis, fibrosis or scarring after surgery.⁴⁵ Strictures are classified as membraniform or tubular by shape, relative or definite by degree and benign or malignant by pathology. In Asia there is a high incidence of

strictures due to repeated hepatolithiasis and cholangitis.⁴⁶ A comet tail sign generally refers to the calculi combined with a stricture; when this is present, dilatation with a balloon (Figure 2(a–c)), bougie⁴⁷ or wire-guided needle-knife electrocautery⁴⁸ are frequently used as therapeutic modalities. Generally, standard balloon dilatation (balloon diameter: 6–12 mm; length: 4 cm; pressure: 8–18 atm; OptiMed, Berlin, Germany) is the first choice recommended for strictures, assisted by other methods.⁴⁹ The yellow Zebra guide wire (Boston Scientific, Boston, USA) is inserted into the strictured bile duct, guiding the insertion of the balloon dilatation catheter, to ensure the catheter occupies the length of the strictures.⁵⁰ Bougie dilatation is indicated as an efficient method to treat strictures.⁵¹ Wire-guided needle-knife electro-incision appears to be effective for traversing refractory biliary or pancreatic strictures.⁴⁸ Repeated basket extraction of calculi beyond the stricture site is an efficient bridge to dilate the bile duct for further balloon dilatation and stenting (Figure 2(d–f)). It is mandatory to stent after dilatation for hepatolithiasis with strictures to prevent re-stricture, bile stasis and reformation of calculi.⁵² The biliary stents for dilatation and drainage are self-made, formed by T-tubes

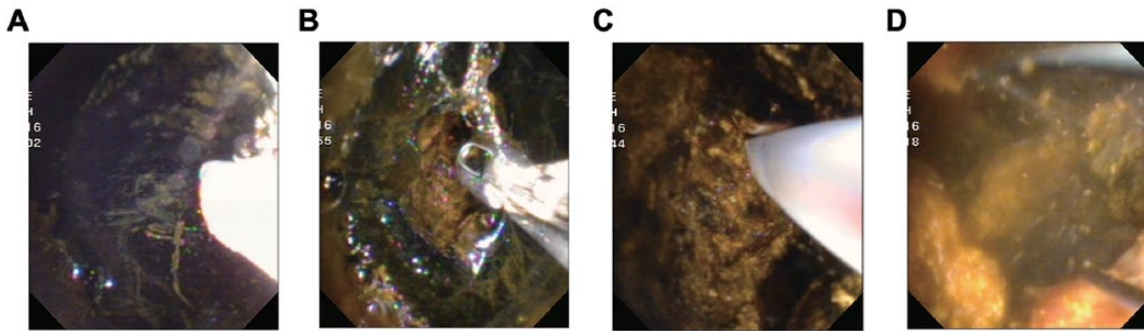


Figure 3. A step-by-step strategy for calculi extraction by combining the methods of biopsy forceps, lithotripsy and a basket. When a tough calculus can hardly be fragmented by EHL (a), the biopsy forceps are introduced to first break the tough surface of the calculus (b). The EHL is then used to successfully fragment the calculus through the weak area exposed by the biopsy forceps (c). Finally, the fragmented calculi can be completely extracted by the basket (d).

(from 6 Fr to 16 Fr, Shida, Shanghai, China). We advise the stenting should last for >3 months. Balloon dilatation and stenting are simple and effective procedures to treat biliary strictures; however, the rate of re-stenosis varies, from 4% within 2 years to 45% within 5–7 years.^{53,54}

Calculi taken out with difficulty

In the treatment of residual hepatolithiasis, clinicians usually encounter complicated calculi, which is difficult to extract easily by the basket method because of impaction or large size. Laser lithotripsy and electrohydraulic lithotripsy (EHL) via cholangioscopy facilitate access to the intrahepatic calculi and provide a simple and effective way to disintegrate large or cast-shaped calculi or relieve impaction under direct visualization.⁵⁵ Holmium laser and EHL achieve a high success rate of up to 90% final stone clearance, alongside low complication rates.⁵⁶ We used EHL at 70–90 V, and holmium laser technology with energy levels set at 800 mJ, 15 Hz and 16 W.^{57,58} The tip of the EHL fibre should protrude about 2–3 mm from the scope and be positioned en-face with the calculus.⁵⁹ The flexible laser fibre tip should be positioned at the distal end of the scope, and the endoscope tip should be brought into therapeutic position using its directional controls.⁶⁰ In general, long-protrusion lithotripsy is used for peripheral calculi that the cholangioscopy tip cannot reach. A too-short protrusion of the fibre tip is not recommended as it may cause damage to the lens. Different theories and methods of lithotripsy bring different grades of validity and security.⁶¹ It is reported that laser lithotripsy is

less satisfactory than EHL for the fragmentation of bile duct calculi,⁶² but EHL has a higher risk of duct damage because of poor targeting.⁶³ We prefer to using laser lithotripsy to break up cholesterol impacted calculi and to applying EHL to explode pigment in compact calculi. In some institutions, pneumatic lithotripsy and hyperacoustic lithotripsy are also used. The fragments of the calculi are then pushed by irrigation of physiological saline through the papillary or the sinus. Intracorporeal lithotripsy can be used in conjunction to enhance the efficiency of the treatment.⁶⁴ If lithotripsy fails, slowly clamping by biopsy forceps could be attempt to break the tough surface of the calculi for further lithotripsy (Figure 3). In some cases, when calculus are impacted laterally in the biliary duct, especially in the right posterior or the left external bile duct, it may be difficult to remove even through the combination of several techniques because of the acute angle of the branches beyond the working range of cholangioscopy.⁶⁵

Imperceptible calculi

Hepatolithiasis is challenging for endoscopic surgeons to treat, especially in symptomatic patients without detection of calculi by cholangioscopy.⁶⁶ Advanced imaging techniques would help in the diagnosis and treatment of hepatolithiasis.²⁹ Conventional transabdominal ultrasound (US) and computed tomography (CT) have sensitivities of >80% and specificity for the diagnosis of choledocholithiasis.⁶⁷ CT is more effective than US in demonstrating the presence of biliary obstruction, the level of obstruction and the cause

of the disease.⁶⁸ T-tube radiography and endoscopic retrograde cholangiography could also show intraductal calculi, strictures and decreased peripheral arborization. Magnetic resonance cholangiopancreatography (MRCP) detects calculi with a sensitivity of 80–93% and a specificity of 100%.⁶⁹ A meta-analysis demonstrated that endoscopic US (EUS) and MRCP have no statistically significant difference in specificity and sensitivity in diagnosing choledocholithiasis.⁷⁰ EUS and MRCP are more highly recommended to detect hepatolithiasis than common US and CT.⁷¹ It is also reported that intraductal ultrasonography (IDUS) is equivalent to cholangioscopy in the identification of residual bile duct calculi.^{72,73} Compared with EUS, IDUS has an improved ability to image the proximal biliary and surrounding structures.⁷⁴ Moreover, in recent years, 3D reconstruction has been able to model the liver's vascular system to guide and optimize the endoscopic procedures.⁷⁵ It has the advantages of identifying the presence of bile duct stricture and/or dilatation, defining the level of biliary obstruction and calculi distribution, and the morphology of large vessels and the adjacent organs.⁷⁶ Dong and colleagues⁷⁷ confirming the efficiency and security of operative rigid choledochoscope in treatment of hepatolithiasis. In brief, imaging-guided POC could more efficiently remove perceptible calculi and more accurately target dormant calculi.⁷⁸

Step-by-step strategy of POC

Hepatic resection has been the prior choice for the treatment of hepatolithiasis, because resection removes not only the calculi but also the associated pathologic lesions. Unfortunately, application of partial hepatic resection is difficult when the calculi is not confined to one segment or lobe of the liver. Hence, partial resection is usually accompanied by choledocholithotomy/choledochojejunostomy and subsequent T-tube placement to allow POC therapy.

To better regulate the cholangioscopic operation, we put forward a step-by-step strategy to treat residual hepatolithiasis (Figure 4). Efficient pre-operative preparations promote successful POC. During Stage 1, diagnosis by multiple imaging methods (US/EUS, CT, MRCP, etc.) and observation by cholangioscopy (POC, PTCS, ERCP, etc.) are required to evaluate residual hepatolithiasis, including the function of papillary, the

diameter of each bile duct, location of calculi, the number of calculi and the maximum size of calculus, which is used for strategy choice. It is imperative to ensure the maturation of the T-tube track to avoid bile leakage; at least 4 weeks for patients in general condition, and 12 weeks for patients with diabetes mellitus or malnutrition. Before a session of POC, pre-operative preparation is conducted in a similar manner as for an ERCP.⁷⁹ Patients are given pethidine (50 mg) by intramuscular injection and positioned supine. When the calculi are located in the left lobe, the right lateral decubitus is appropriate for angle manipulation. If it is located in the right lobe, the opposite is recommended.

In patients with T-tube drainage, the fixation is released from the nape, and the T-tube is slowly pulled out to avoid track eversion. The cholangioscope is introduced into the bile ducts through the tracks, and an examination of CBD and intrahepatic bile ducts is conducted to confirm the mucosal condition of the stem and branch tracks and to re-evaluate the distribution, quantity and size of the calculi. In patients with choledochojejunostomy, the cholangioscope is introduced into the afferent loop of the jejunum, and the anastomotic stoma of choledochojejunostomy is confirmed. The same procedure is performed in patients with choledocholithotomy. Persistent irrigation with saline solution is needed to ensure a clear view. If there are strictures in the intrahepatic bile ducts, repeated dilatation and a long period of stenting for drainage should be performed in the next stage. If there are no strictures, the management of calculi is considered. When dealing with the calculi, it is imperative to first irrigate with saline and suction to pull muddy or finely divided calculi out through the sinus, or push them out through duodenal papilla or anastomotic stoma. Subsequently, baskets or grasping forceps are inserted through the accessory sinus of the cholangioscope to remove calculi, the diameter of which is shorter than that of the T-tube track. Third, large or impacted calculi are fragmented by introducing a probe for lithotripsy, and then fragments are extracted by basket through the sinus or pushed into the enteric cavity from the duodenal papilla or the anastomotic stoma. If lithotripsy fails, biopsy forceps are considered for clamping the tough surface to facilitate the follow-up lithotripsy. Repeated manipulations and combinations of the above multiple approaches in the procedure increases

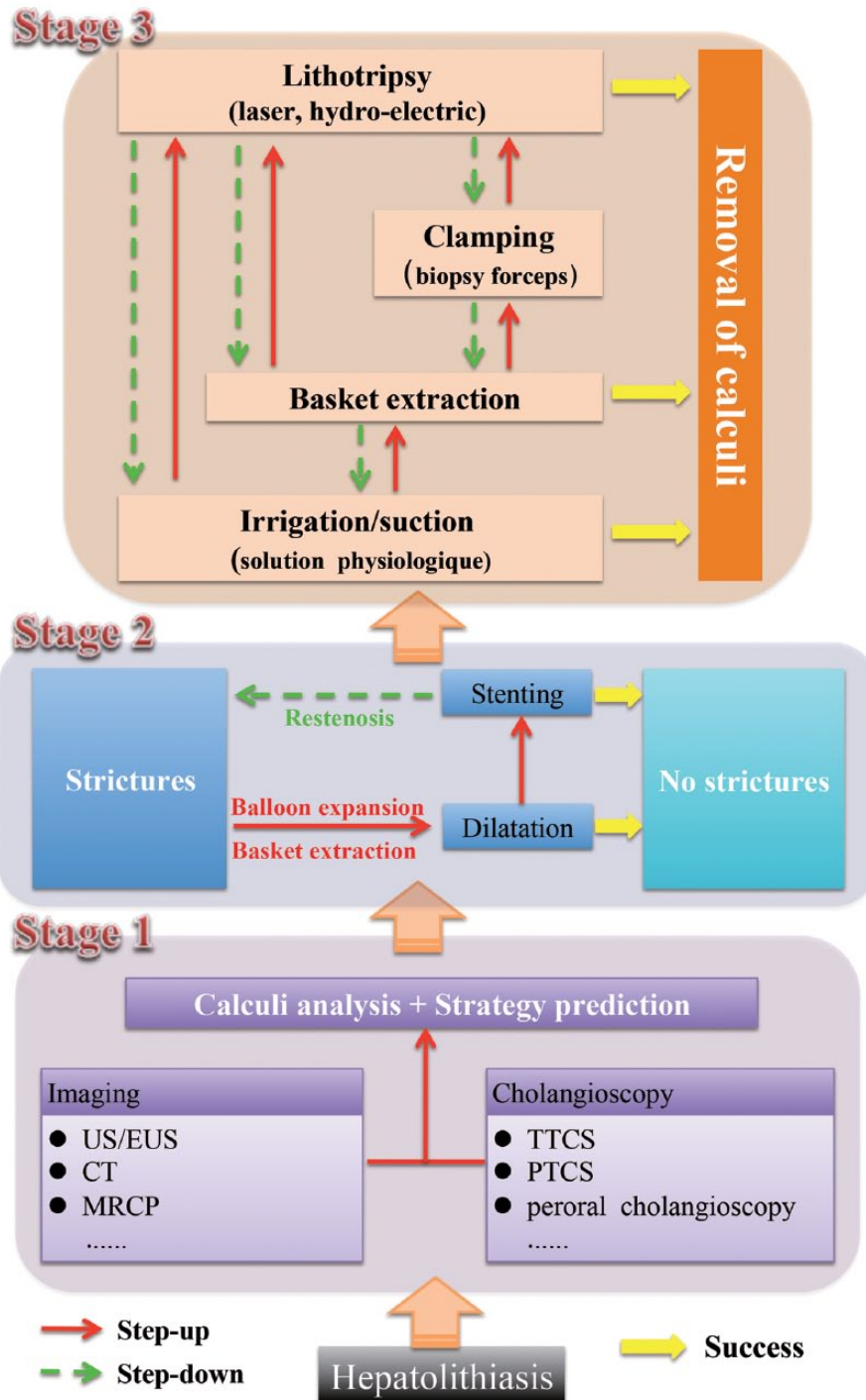


Figure 4. Flow chart of step-by-step strategy for management of hepatolithiasis under post-operative cholangioscopy (POC). Three stages are established for the management of hepatolithiasis. Stage 1 consists of the imaging methods and POC for analysing the calculi situation and making a strategy choice. Stage 2 aims to relieve strictured bile ducts. Stage 3 is to remove the calculi by a combination of: irrigation/suction of saline solution under different pressure, extraction with a basket, lithotripsy via laser or hydroelectric, clamping through biopsy forceps.

CT, computed tomography; MRCP, magnetic resonance cholangiopancreatography; PTCS, percutaneous transhepatic cholangioscopy; TTCS, T-tube track cholangioscopy; US/EUS, Ultrasound/Endoscopic ultrasound.

Table 1. The POC operational methods in management of residual hepatolithiasis.

Calculus categories	Operational methods					Complete removal rate (%)	Recurrence rate (%)
	Irrigation/suction	Basket extraction	Forceps grasping	Lithotripsy	Lithotripsy+clamping		
Size (mm)							
diameter ≤1	X					100	8.90
1 < diameter ≤ 5		X	X			96.80	6.30
diameter > 5		X	X	X	X	95.30	7.50
Property							
Muddy	X	X				100	7.80
Moderate		X		X		94.60	5.20
Tough		X	X		X	93.20	3.30
Impaction							
Yes				X	X	92.40	12.20
No	X	X	X	X	X	96.70	5.30

the rate of clearance. POC operational methods in management of residual hepatolithiasis are summarized in Table 1, according to the size, property and impaction of the calculi. A catheter is placed when repeated procedures (at least 1 week interval) are required.²⁵ Antibody and transamin are generally used post-lithotripsy in cholangioscopy if there is poor-condition mucosa to prevent cholangitis and haemorrhage.

Complications related to POC

It has been reported that overall complications of cholangioscopy range from 5 to 54%, with an average rate of 22%.⁸⁰ A Japanese questionnaire survey reported that the most frequent complication was recurrent calculi, followed, in order, by cholangitis, liver abscess and cholangiocarcinoma.⁸¹ With improved instruments and skilled endoscopists, the incidence of complications has decreased.

Complications are classified as symptoms (fever, vomit, diarrhoea, haemobilia) and signs (infection, sinus perforation, T-tube herniation, sinus tightening). Although miscellaneous complications occur in/after POC, the most common complications are haemobilia and infection, occurring in around 8% of cases.^{27,80} Bleeding may obscure the visual field, prolong the manipulation time and reduce procedural success in the session. The main reason for bleeding could

be inflamed mucosa from prior cholangitis or the compression of impacted calculi; another reason is the friction between the cholangioscope/basket and friable ductal walls or untargeted lithotripsy.^{26,82} Bleeding is generally treated by tamponading with the cholangioscope body or balloon, soaking with haemostatics (norepinephrine), coagulation with an electronic surgical workstation, blockage with stents and occlusion with haemostatic clamps.⁸³ Haemostatics should not be irrigated directly into the bleeding site in case of hypertension or tachycardia. If bleeding persists, the procedure should be terminated and a catheter should be placed to allow future sessions. Meanwhile, the drain should be watched carefully until it is clear. In addition, step-down decompression is a good method for preventing haemobilia after dilatation.²⁵ Transient fever and pain can be released in most cases by persistent drainage.⁸⁴ Vomiting usually results from the stimulation of cholangioscopy and manipulation to bile ducts.⁸⁵ It is compulsory for patients to be NPO before POC to avoid the aspiration of food residue. Most cases of diarrhoea are due to irrigation of too much saline solution to the intestines, which should be limited in the session.⁵⁴

It is not advised to manipulate before adequate biliary drainage is achieved to clear the infected bile. Localized infections such as intrahepatic abscess, sub-phrenic abscess and biliary

peritonitis can be treated by puncture drainage guided by US or CT.⁸⁶ General antibiotics are commonly used to deal with the infectious complications. Incomplete extraction of the T-tube leads to obstruction, sinus hypoplasia and sinus atresia.⁸⁷ Suitable placement of the T-tube can reduce the length of sessions and prolong the drainage time. Repeated POC is a risk factor for T-tube extraction, and prolonged retention of T-tube increases the occurrence rate of residual calculi.²⁵ Hence, the placement principle of 'short, thick and straight' should be followed, which means the distance from bile duct to abdominal wall is short, the path is straight and T-tube is as thick as possible.⁸⁸ Sinus fracture or sinus perforation occurs because of the violent extraction of calculi with the basket. Placement of the catheter along the sinus ensures unobstructed drainage for at least 4 weeks for sinus maturation.⁸⁹ To prevent the passageway from skin to bile duct breaking off, based on our previous clinical data, a guide wire (COOK, Bloomington, USA) should be inserted into the T-tube before its extraction. Once the tube is extracted and the sinus is incomplete or stricture, it is recommended to place a guide wire under radiography to make a bridge between the two ends or to provide a wizard to place a new T-tube.

Summary

POC is a safe and effective treatment for residual hepatolithiasis. To regulate the cholangioscopic operation, we put forward an approach to manage strictures and imperceptible calculi. With a more thorough understanding of normative operation and advanced techniques, there remains opportunity for endoscopists pursuing better therapy for hepatolithiasis and fewer complications for patients.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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