Modern Medicine. 2015, Vol. 22, No. 2 : 144-150 

Review

# Modern Management of Benign Bile Duct Strictures

**Cristian Balahura[1,2], Petre Iacob Calistru[1,3], Gabriel Constantinescu[1,2]**

[1]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2]"Floreasca" Clinical Emergency Hospital, Bucharest, Romania
[3]"Dr. Victor Babeș" Infectious and Tropical Diseases Hospital, Bucharest, Romania

## REZUMAT

***Managementul modern al stenozelor biliare benigne***

Stenozele biliare benigne reprezintă o patologie cu abordare diagnostică și terapeutică deseori dificilă. În trecut principalul tratament în majoritatea cazurilor era chirurgical. Astăzi terapia endoscopică este preferată având în vedere că este minim invazivă, poate fi repetată și are rate reduse de morbiditate. Colangiografia endoscopică retrogradă (ERCP) este utilă pentru stabilirea diagnosticului și realizarea dilatării și stentării stenozei. Inserția temporară de stenturi biliare de plastic multiple reprezintă tratamentul endoscopic standard. Eficiența utilizării stenturilor biliare metalice expandabile neacoperite este în curs de evaluare. Majoritatea stenozelor biliare benigne apar în evoluția pancreatitei cronice, după colecistectomie sau după transplant hepatic. Rezultatele terapiei endoscopice diferă în funcție de etiologia stenozei. Deși nu este eficient în toate cazurile, tratamentul endoscopic are un profil de siguranță acceptabil și este prima linie de abordare a stenozelor biliare benigne. El poate fi util ca "punte" către tratamentul chirurgical în unele cazuri de pancreatită cronică sau stenoze post-transplant hepatic.

**Cuvinte cheie:** stenoze biliare, ERCP, pancreatită cronică, colecistectomie, transplant hepatic

## ABSTRACT

The diagnosis and treatment of benign biliary strictures (BBS) are often challenging. In the past, surgery was the treatment of choice in the majority of cases. Nowadays the endoscopic treatment of BBS is preferred over surgery because it is less invasive, repeatable and associated with lower morbidity rates. The endoscopic retrograde cholangiopancreatography (ERCP) can make the diagnosis of the stricture, and provide its dilation and stent placement. Temporary insertion of multiple side-by-side large-bore plastic stent is the standard of care in endoscopic therapy. The use of uncovered self-expanding metal stents is under investigation. Most commonly BBS occur in the evolution of chronic pancreatitis, and after liver transplant or cholecystectomy. The efficacy of endoscopic therapies is different and depends on the cause of BBS. Though it has limitations, endoscopic therapy has a favourable safety profile and remains a first-line management option in benign biliary strictures.

**Corresponding author:** Balahura Cristian, MD
Clinical Emergency Hospital Bucharest
8, Floreasca Street, 014461, Bucharest, Romania
e-mail: cristian.balahura@gmail.com

Endoscopic therapy may be considered a bridge to surgery in some cases of chronic pancreatitis or in non-anastomotic strictures after liver transplant.

**Key words:** biliary strictures, ERCP, chronic pancreatitis, cholecystectomy, liver transplant

## INTRODUCTION

Benign biliary strictures (BBS) are a heterogeneous group of disorders whose diagnosis and treatment may be challenging. Surgical injury of the bile duct is the most common cause in the Western world (1). Inflammatory lesions of the biliary ducts, such as chronic pancreatitis represent the second most common cause of BBS.

The appropriate evaluation and management frequently require collaboration between gastroenterologists, surgeons and radiologists. The confirmation of the stricture is preferably made by magnetic resonance cholangiopancreatography (MRCP). A mainstay of diagnosis is the differentiation of BBS from malignant obstructions which are more prevalent. Tissue sampling during ERCP or endoscopic ultrasound with fine needle aspiration can be useful.

BBS have different causes, with specific evolutions and management strategies. The ethiologies of BBS are presented in **table 1** (2).

The clinical presentation of a biliary stricture depends on the severity of the obstruction. The disease may be subclinical, associated with mild increase of liver function tests or may present with complete biliary obstruction, jaundice and sometimes cholangitis. Delayed presentation may be seen especially with ischemic bile duct injuries. In these cases symptoms may develop years after the initial insult.

### Classification

Two classification systems are commonly used for the characterization of BBS. The most commonly used is the Bismuth classification which is based on stricture location. Strasberg classification considers bile leakage, location, and size of the stricture (3-5).

### Endoscopic therapy for BBS

Endoscopic retrograde cholangiopancreatography (ERCP) is the therapeutic intervention of choice in patients with biliary strictures. After selective biliary cannulation of the bile duct a cholangiogram is obtained. The diameter and length of the stricture is estimated. Cytology should be obtained to confirm benignity. Then a dilation of the SBB by either balloon or bougie is done under fluoroscopic guidance. Balloons with diameters between 4-mm and 12-mm are used. Insertion of multiple side-by-side large-bore plastic stents is the standard of care in endoscopic therapy (**Fig. 1**) (6). This achieves the highest long-term biliary patency rate (5, 7, 8). Periodic dilation and stent exchange with placement of additional stents are performed every 3 to 4 months during the next year. Up to 5 or 6 stents can be finally placed. Clinical success was observed in 94% of cases after side-by-side placement of multiple plastic

**Table 1. Causes of benign biliary strictures**

| | |
|---|---|
| **Postoperative strictures** | • cholecystectomy |
| | • hepatic resection |
| | • orthotopic liver transplant |
| | • biliary-enteric anastomosis |
| | • percutaneous therapy for hepatocellular carcinoma |
| **Inflammatory** | • chronic pancreatitis |
| | • primary sclerosing cholangitis |
| | • choledocholithiasis |
| | • autoimmune cholangiopathy (Ig G4 - associated) |
| | • vasculitis |
| | • radiation therapy |
| **Infectious** | • recurrent pyogenic cholangitis |
| | • parasitosis: Ascaris lumbricoides, Clonorchis sinensis, Opisthorchis viverrini |
| | • granulomatous: tuberculosis, histoplasmosis |
| | • viral: cytomegalovirus, human immunodeficiency virus |
| **Ischemic** | • hepatic artery thrombosis and stenosis |
| | • portal biliopathy |
| **Other** | • abdominal trauma |
| | • Mirizzi syndrome |
| | • post-biliary sfincterotomy |

**Table 2. Bismuth classification of BBS**

| Bismuth classification | Location |
|---|---|
| I | >2 cm distal to hilum |
| II | <2 cm distal to hilum |
| III | hilar involvement but confluence preserved |
| IV | confluence involved, with no communications between left and right hepatic ducts |
| V | type I, II or III and stricture of an isolated right duct |

**Table 3. Strasberg classification for BBS**

| Strasberg class | Description |
|---|---|
| A | injury to small ducts in continuity with biliary system, with cystic duct leak |
| B | injury to sectoral duct with consequent obstruction |
| C | injury to sectoral duct with consequent bile leak from a duct not in continuity with biliary system |
| D | injury lateral to extrahepatic ducts |
| E1 | stricture located >2 cm from bile duct confluence |
| E2 | stricture located <2 cm from bile duct confluence |
| E3 | stricture located at bile duct confluence |
| E4 | stricture involving right and left bile ducts |
| E5 | complete occlusion of all bile ducts |

stents but in only 60% of cases if one single plastic stent was used. Complications occurred in 20% of cases after insertion of multiple plastic stents and in 36% of patients with single plastic stents (9). BBS recurrences can be re-treated by ERCP.

Self-expanding metal stents (SEMS) can provide a diameter 3 times higher than standard 10-Fr plastic stents. They have small delivery systems so no aggressive dilation of the BBS is required before insertion. These stents do not require successive procedures to achieve an adequate dilation of the stricture. There are 3 types of biliary SEMS: uncovered, partially covered and fully covered.

Use of uncovered SEMS for BBS in postorthotopic liver transplant (post-OLT) biliary strictures, postsurgical strictures and chronic pancreatitis was associated with clinical success rates of 50%, 60% and 80% respectively (10-12). The complication rate after uncovered SEMS placement is as high as 40% (9). The median patency of uncovered SEMS is approximately 20 months. Stent occlusion from reactive tissue hyperplasia is their main complication. Reinterventions are needed in these cases to solve stent obstruction. Uncovered SEMS usually become embedded into the bile duct wall, so they are not removable (13). For these reasons uncovered SEMS are not indicated in the management of BBS (9).

Fully covered SEMS (FCSEMS) have a prolonged duration of patency because occlusion from reactive tissue hyperplasia and embedding into the bile duct are prevented. This stents have an initial success rate of about 80-90%. Their main complication is stent migration, reported in 5 to 33% of cases (14, 15). Biliary reobstruction, bowel perforation or obstruction occur more frequently compared with plastic stents.

Partially covered SEMS (PCSEMS) have uncovered proximal and distal ends. This decreases the risk of migration but increases the rate of tissue embedment, leading to difficulties in stent removal. One year after PCSEMS insertion, stricture resolution was reported in 75% and stent migration in 14% of patients (16).

Temporary insertion of FCSEMS/PCSEMS is under investigation in long-term follow-up studies.

Hilar and intrahepatic strictures can be difficult

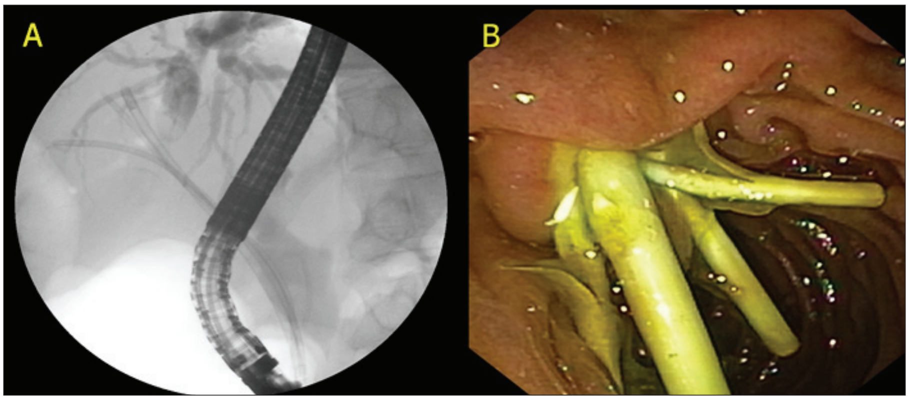


**Figure 1.** Multiple side-by-side plastic stents in place. Radiological (A) and endoscopic (B) aspects.


**Figure 2.** Post-cholecystectomy stricture. (A) Initial ERCP shows narrowing of the bile duct and metalic clips placed nearby. (B) Insertion of a guidewire proximal to the stricture. (C) Insertion of a biliary plastic stent across the stricture.

to manage endoscopically and in these cases the drainage can be realized by percutaneous trans-hepatic cholangiography.

*Postoperative bile strictures*

Cholecystectomy (CCY) has a risk of 0,5% for development of BBS (17). The most common cause of injury is the confusion of the cystic duct with the CBD. Other causes include electrocautery injury, thermal injury to CBD, traction on the gallbladder neck and biliary ischemia (18). The complication may manifest early in the postoperative period with jaundice and cholangitis or with bile leak and peritonitis. After ischemic injury the presentation is usually delayed.

Most BBS can be managed endoscopically but complete occlusion or transection of the common bile duct (CBP) usually requires surgical treatment. The standard endoscopic approach to post-CCY biliary strictures consists in the insertion of 2 or more plastic stents which are exchanged every 3 months for at least a 12-month period (**Fig. 2**) (7, 19). At the end of 12 months of treatment a success rate of 74% to 90% was reported. Still, within 2 years of stent removal the stricture recurred in 20% to 30% of cases (5, 19). Proximal hilar lesions (Bismuth III) are associated with worse outcomes compared with distal strictures (Bismuth I and II) (25% vs 80%, respectively) (5). A long-term follow-up of 13 years after endoscopic treatment of post-CCY strictures reported stricture recurrence rates of 11,4% (20).

*Chronic pancreatitis-associated biliary strictures*

Distal BBS may occur in 25% of patients with chronic pancreatitis. Biliary decompression is indicated in these cases to prevent secondary biliary cirrhosis, choledocholitiasis, and cholangitis(21). These patients are often poor surgical candidates, so endoscopic therapy is a lower-morbidity alternative (22). Endoscopic insertion of multiple plastic stents provides a long-term biliary patency rate of 65%, better than single plastic stent placement (**Fig. 3**).

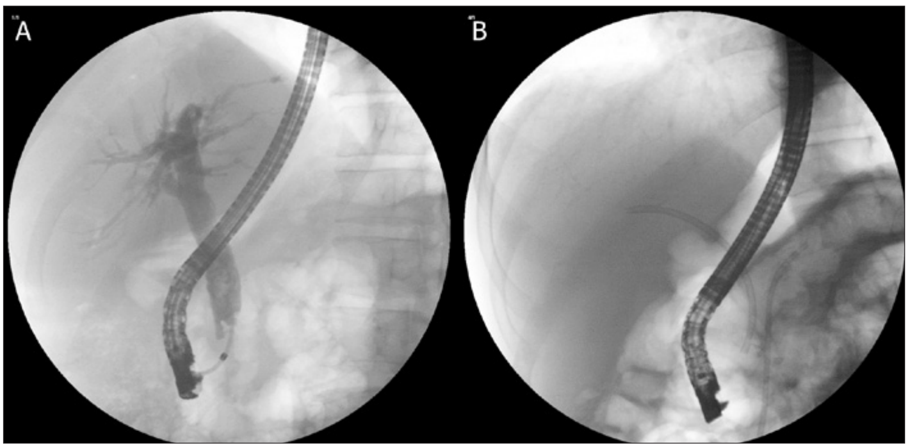


**Figure 3.** Stricture caused by chronic pancreatitis. (A) Initial ERCP shows narrowing of the distal bile duct. (B) Biliary and pancreatic plastic stents in place

Temporary simultaneous placement of multiple plastic stents is the standard of care endoscopic therapy (21). Because of the pancreatic fibrosis, BBS associated to chronic calcifying pancreatitis are more resistant to dilation via stenting (23). After endoscopic treatment, the stricture relapses in 33% of patients (24).

In patients with chronic pancreatitis, 6 months after PCSEMS insertion, stricture resolution was achieved in 90% of cases with a recurrence rate of 20% after 22 months (25).

Though with lower morbidity rates, the results of endoscopic therapy are less durable than surgery. Endoscopic dilation and stenting may be considered as bridge therapy for patients who are fit for surgery (26).

### *Post-liver transplant strictures*

OLT is the procedure with the highest risk of developing postoperative BBS with a rate of 20 to 30% (27). BBS are the most common complications of OLT and may have different presentation times. Early strictures develop in the first 30 days after OLT, are often located at the anastomosis and may be caused by CBD diameter mismatch between the donor and recipient. The risk is higher after hepaticojejunostomy than after duct-to-duct anastomosis. Late strictures develop more than 30 days after OLT and are associated with ischemic damage. These lesions require longer duration of endoscopic therapies and are associated with higher rates of retransplantation and surgical revision (28).

There are two types of post-OLT biliary lesions: anastomotic strictures (AS) and nonanastomotic strictures (NAS).

AS represent about 80% of post-OLT strictures. The characteristic aspect of AS is a single, short stricture in the middle portion of CBD (29). Endoscopic treatment with balloon dilation and stenting was associated with long-time resolution of AS in 70 to 100% of cases. Thus balloon dilation and stenting of AS were more effective than balloon dilation alone (30). Placement of multiple side-by-side plastic stents is recommended (31). Two months after placing a PCSEMS, strictures were effectively dilated in 86% of cases. However difficulties in stent removal and a high recurrence rate of 50% were reported. At short-term follow-up (< 2 years) persistent stricture dilation after FCSEMS was reported in 50-80% of patients (**Fig. 4**) (32). Early AS (within the first 1-2 months after OLT) respond better to endoscopic dilation with stent insertion and in most of these cases stricture resolution is achieved after 3 months (33). Late AS require endoscopic stenting for 12 to 24 months, with stent exchange every 3 months.

NAS count for 10 to 25% of all post-OLT strictures (34). Nonanastomotic stenoses are multiple, diffuse and located proximal to the anastomosis, at the level of the hilum or in the intrahepatic biliary ducts (35). They usually are associated with ischemic injury to the biliary tree, after prolonged donor organ ischemic time and hepatic artery thrombosis or stenosis (36). The diagnosis of NAS is usually made 10 months after OLT (37). Three year follow-up after OLT showed an incidence of NAS of 37% when the transplanted liver was donated after cardiac death and a rate of 12% when the donation was made after brain death and life-support (38). The prognosis of these patients is poor. Long-term response after endoscopic therapy of NAS is

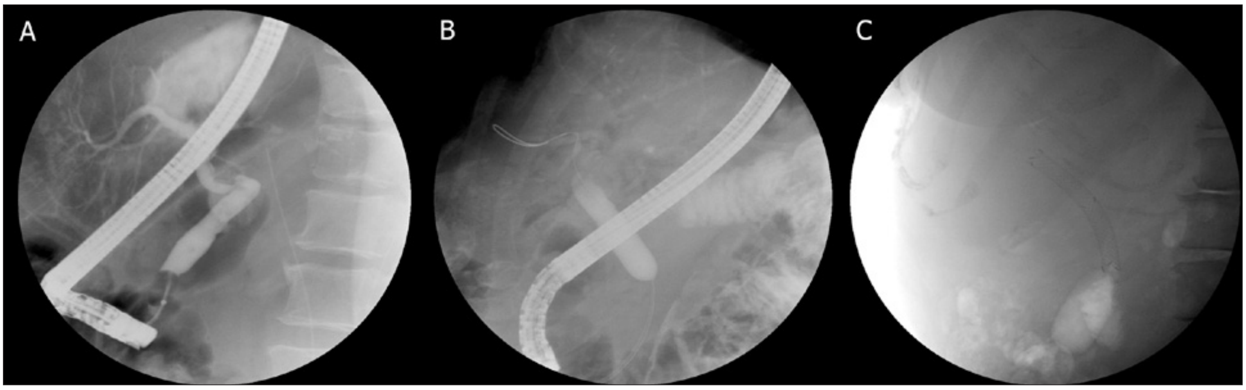


**Figure 4.** Post–liver transplant stricture. (A) Initial ERCP shows narrowing of the bile duct. (B) Balloon dilation of the stricture. (C) SEMS advanced across the stricture

reported in 50% to 75% of cases and 25-50% of patients need retransplantation. Therefore endoscopic dilation and stenting for NAS are considered a bridge to retransplantation (39).

### *Primary sclerosing cholangitis (PSC)*

Dominant strictures develop in 40% of patients with PSC (40). Stent placement is not recommended in these cases because stent occlusion and cholangitis are frequent. Endoscopic balloon dilation from 18 to 24 Fr diameter is indicated and routine periprocedural antibiotic prophylaxis of cholangitis should be considered (41). PSC carries a 20-30 % risk of developing cholangiocarcinoma, so strictures should be brushed for cytology (42).

### *Biliary-enteric strictures*

Biliary-enteric strictures may occur after partial liver resection, Whipple pancreaticoduodenectomy or OLT with Roux-en-Y hepaticojejunostomy. Endoscopic therapy in these cases is difficult because of the postoperative enteral anatomy. Colonoscopes or balloon enteroscopes can be used to reach the stricture and perform balloon dilation and stent placement. In patients with Roux-en-Y anatomy, the reported technical success rate of single-balloon ERCP was 70% (43). Early dilation of anastomotic strictures (within 30 days after surgery) is associated with a high risk of perforation and consequent bile leak. In these cases smaller balloons/bougies should be used (30).

## CONCLUSIONS

BBS have diverse causes including postoperative complications, chronic pancreatitis and liver transplant. Endoscopy therapy with balloon dilation and stent insertion is the therapeutic gold standard. The endoscopic management usually involves side-by-side placement of multiple plastic stents with 3-month exchange of these stents for 1 to 2 years. SEMS are under investigation for this indication. Underway clinical trials are expected to establish the best approach.

## Acknowledgement

This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/159/1.5/S/137390.

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