

### Different Modalities in the Management of Post Hepaticojejunostomy Biliary Stricture

Mohammed Siam, Samir Ibrahim, Hatem Mohammed, Mohamed Farouk General Surgery Department, Faculty of Medicine, Zagazig University, Egypt. Corresponding author: Mohammed Siam, Email: <u>mohammedsiam130@gmail.com</u>

#### ABSTRACT

Biliary reconstruction with biliary-enteric anastomosis is frequently required in patients with benign and malignant illness of the hepatobiliary pancreatic area. One of the biliary-enteric anastomosis's long-term consequences, cholangiosis can necessitate numerous hospital stays and surgical procedures. Hepaticojejunostomy stricture is a serious complication of biliary surgery, if untreated, can lead to repeated cholangitis, biliary cirrhosis, hepatic failure and eventually death. Operations requiring biliary-enteric anastomosis are uncommon, and the true incidence of postoperative stricture is unknown. Factors that predict anastomotic stricture include proximal biliary stricture, multiple prior attempts at repair, intra-abdominal abscess or bile collection, external or internal biliary fistula, and anastomosis in an undilated duct. Some benign biliary strictures are idiopathic. Revision hepaticojejunostomy being a complex procedure will be difficult by the sequelae of long-standing unrelieved biliary obstruction like portal hypertension due to secondary biliary cirrhosis, atrophy of liver lobes and presence of cholangiolytic liver abscess with the success rate of surgical repair decreases with each successive surgical intervention. In addition, there is a need for additional reliable data to analyse and comprehend the impact of a cholangitis on patients' quality and length of life given the dearth of reports on post-hepaticojejunostomy cholangitis. Therefore, this study aimed to review the different modalities in the management of post hepaticojejunostomy biliary stricture.

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#### Introduction

Biliary stricture (BS) is one of the most problematic adverse events.Endoscopic treatment with endoscopic retrograde cholangiography (ERC) is the first-choice treatment for BS with duct-to-duct anastomosis, which occurs in 24.3-31.7% of patients. Other alternatives include endoscopic treatment, percutaneous transhepatic biliary drainage (PTBD), and re-surgery (1,2).

Proximal biliary stricture, many failed efforts at repair, intra-abdominal abscess or bile collection, external or internal biliary fistula, and anastomosis in an undilated channel are all risk factors for anastomotic stricture**(3)**. A precarious side effect of biliary surgery is hepaticojejunostomy stricture, which, if left untreated, can result in recurrent cholangitis, biliary cirrhosis, hepatic failure, and eventually death(4).

In general, anastomotic strictures that occur early in the postoperative period are usually secondary to surgical technical issues or postoperative bile leak, whereas those that appear later are most likely due to fibrotic healing (5).Postoperative stricture formation at the anastomotic site varies throughout the literature from 4 to 38% of patients (6).



# Diagnosis of post hepaticojejunostomy biliary stricture:

#### I) Clinical presentation:

Patients with post-anastomotic biliary strictures is generally the result of obstruction to bile outflow, although cholangitis can supervene in a minority of cases. The clinical findings can include jaundice, right upper quadrant pain, fever, and pruritus (5). Biliary obstruction may lead to common bile duct stones and even biliary cirrhosis in chronic cases. Some patients may present with nonspecific symptoms (fever and anorexia) (7).

#### **II)** Laboratory investigations:

The liver profile may show a cholestatic pattern, with elevated alkaline phosphatase (ALP) and yglutamyltransferase (GGT) levels, elevated direct bilirubin levels, and mildly to moderately elevated transaminase levels (5).

Coagulopathy which may manifest itself with a prolonged prothrombin time due to impaired absorption of the fatsoluble vitamin K as a result of failure of bile salts to reach the intestine in cases of biliary obstruction **(8)**.

The serum albumin may be decreased due to chronic illness and may even indicate early cirrhosis. Jaundiced patients must kept well hydrated for their susceptibility to renal impairment which should be tested along with tests for hepatitis viruses, particularly hepatitis C that may have been contracted from blood transfusion **(9)**.

#### III) Imaging investigations:

#### a. Abdominal Ultrasonography:

It is considered the first step in the diagnostic work-up of patients with abdominal complaints after biliary operations is ultrasonography which can detect a fluid collection, bile duct dilatation and gross modifications of hepatic parenchyma. It also can facilitate subsequent percutaneous aspiration of the bile, which will establish the diagnosis and its drainage (10). Ultrasonography can accurately detect dilatation of intrahepatic and extrahepatic bile ducts, thus providing indirect evidence for the presence of bile duct strictures. However, sonography is less accurate for determining the etiology and level of obstruction. The sensitivity of US also depends on the degree of obstruction and has been found to be 94% with a serum bilirubin level of more than 10 mg/dL but only 47% with bilirubin levels of less than 10 mg/dL(8).

# b. Endoscopic ultrasonography (EUS):

It uses specially designed а endoscope with an ultrasound transducer at its tip which allows visualization of the liver and biliary tree from within the stomach and duodenum. Thus, it accurately determines the cause of biliary obstruction with the added benefit of allowing for tissue sampling with cytologic brushings, fine needle aspiration or even stent insertion can also be performed (11).

### c. Magnetic resonance cholangiopancreatography (MRCP):

Visualization of the biliary tract by MRCP, not only will establish the diagnosis, but it also identifies the nature and level of lesion **(12)**.Since its introduction, MRCP has rapidly become an indispensable tool for visualizing the biliary system. It takes advantage of the fact that bile has a high signal intensity image, whereas the surrounding structures do not and can be suppressed



during image analysis. The presence of biliary dilatation can be accurately detected by MRCP in 97-100% of cases with the level of obstruction being correct in almost 87% of patients**(Figure**  **1)**. MRCP provides a valuable alternative to ERCP that allows imaging of the biliary tree even when ERCP is not successful. Unlike ERCP, it is not therapeutic **(10)**.



Figure (1): Proposed management algorithm of patients presenting after creation of a biliary-enteric anastomosis. Depending upon the patient's presenting symptoms, use of

MRCP or percutaneous transhepatic cholangiography are reasonable studies in the evaluation of an anastomotic stricture

#### d. Computed Tomography (CT):

Spiral computed tomography (SCT) and multidetector CT (MDCT) scanning are highly sensitive for the diagnosis of biliary obstruction and intrahepatic and extrahepatic bile duct dilatation, particularly when these modalities are performed with oral and intravenous contrast agents. However, the main value of CT scanning is its ability to detect the site of obstruction with greater accuracy than US and to help predict the cause of obstruction and also provides the benefit of detecting metastatic lesions in the case of malignancy as well as detecting any associated complications (13).

Positive Contrast enhanced CT Cholangiography is CT of the biliary tract that is enhanced with use of positive biliary contrast material which can be introduced invasively with direct injection into the bile ducts via a percutaneous transhepaticbiliary ERCP. catheter Alternatively, or noninvasive opacification of the biliary tract can be done using intravenous contrast materials that are excreted into the bile. Its use is restricted and uncommon because of potentially lifethreatening allergic reactions (14).

## e. Hepato-biliary scintigraphy (HIDA scan):

Technetium-99m -labelled derivatives of iminodiacetic acid (HIDA) when injected intravenously are selectively taken up by the retroendothelial cells of the liver and excreted into the bile. This allows for visualization of the biliary tree and gall bladder. Non-visualization of the gall bladder suggestive of is acute cholecystitis and may be reduced or delayed in chronic cholecystitis. Biliary



scintigraphy may also be helpful in diagnosing bile leaks and iatrogenic biliary obstruction and can identify and quantitate the leak thus helping the surgeon determine whether an operative or conservative approach is warranted. Subjects with severe jaundice are not candidates for radionuclide imaging. This method is helpful in the follow-up of patients who have undergone repair of a bile duct stricture **(15)**.

### f. Endoscopic retrograde cholangiopancreatography (ERCP):

ERCP is a valuable technique in biliary disease because it has both diagnostic (e.g., sphincter of Oddimanometry) and therapeutic functions (e.g., stone extraction, biliary drainage, stent placement) that can be carried out at the same time as the primary diagnosis. The success rate of ERCP is often 90-95% and with a complication rate of approximately 3-5%, ERCP can help detect intrahepatic and extrahepatic biliary dilatation, stones, and the site of biliary stricture with the highest sensitivity and specificity (both approximately 90-100%). ERCP can help differentiate malignant from benign biliary obstruction and even infectious causes of biliary obstruction can be diagnosed using collected bile samples or brushings (16).

## g. Percutaneous transhepatic cholangiography (PTC):

PTC is indicated in cases of biliary strictures in the presence of biliaryenteric anastomosis (e.g., Roux-en-Y hepaticojejunostomy,

choledochojejunostomy, Billroth II gastrectomy), the presence of complex hilar strictures, or when ERCP is unsuccessful. It has success rate that approaches 100% when ducts are dilated. Therapeutic intervention, including biliary drainage, dilation of benign bile duct strictures, extraction of biliary tract stones, or placement of a stent across a malignant stricture also can be performed at the same time. PTC is contraindicated in patients with bleeding diathesis and significant ascites (16).

This is an invasive technique in which the bile ducts are cannulated directly and only undertaken once a bleeding tendency has been excluded and the patient's prothrombin time is normal. Antibiotics should be given prior to the procedure. Under radiological control (either ultrasound, fluoroscopy, or CT), a bile duct is cannulated after, a needle (the Chiba or Okuda needle) is introduced percutaneouslyinto the liver substance. Successful entry is confirmed by contrast injection or aspiration of bile. Water-soluble contrast medium is injected to demonstrate the biliary system and multiple images can be taken demonstrating areas of strictures or obstruction. Bile can be sent for cytology. This technique can also enable placement of a catheter into the bile ducts to provide external biliary drainage or the insertion of indwelling stents. The scope of this procedure can be further extended by leaving the drainage catheter in situ for a number of days and then dilating the track sufficiently for a fine flexible choledochoscope to be passed into the intrahepatic biliary tree in order to diagnose strictures, take biopsies and remove stones. In general, if a malignant stricture at the level of the confluence of the right and left hepatic ducts or higher is suspected in a jaundiced patient, a PTC is preferred to ERCP as successful drainage is more likely (17).

h. Fistulography:

In postsurgery patients with an external biliary fistula or T tube, contrast medium can be injected into the biliary system through the tube or the fistula. This outlines the intrahepatic and extrahepatic bile ducts and demonstrate the site of stricture and the anatomy of the fistula. This procedure may cause cholangitis; therefore, patients should receive antibiotic prophylaxis **(16)**.

### Interventional procedures of post hepaticojejunostomy biliary stricture:

Cases with cholangitis that fail to improve with conservative treatment usually require urgent decompression of the obstructed biliary system. Treatment options for bile duct strictures include endoscopic or percutaneous balloon dilatation and insertion of an surgery endoprosthesis or (16).Percutaneous treatment by balloon dilatation followed by shortto intermediate-term stent placement seems to provide a more durable result (18).

#### I) Endoscopic management:

Endoscopic management is the least invasive very effective via either balloon dilatation or stenting of the stricture. The major obstacle for endoscopic access is the altered anatomy of the Roux-en-Y construction. Endoscopy can be done using double or single balloon enterostomy to overcome this difficulty which is difficult and time consuming. Surgical access loop is constructed to be used by the endoscopist to reach the HJ stoma. These access loops could be jejunocutaneous either superficial or subfacial, jejunal loop interposition, jejunoduodenostomy or gastric access loop (19).

Endoscopic retrograde balloon dilatation: a procedure that may facilitate both multiple stent placement and use of lithotripsy, however, currently only provides success rates of 70 % cases using single-balloon enteroscope. Finally, the "rendez-vous" technique, which combines both endoscopic and percutaneous approaches, may be useful in complex situations. However, in a setting of HJ stricture, this strategy remains clearly marginal with only limited reported experience (19).

The introduction of the double balloon enteroscope (DBE) in 2001 has allowed endoscopic access into the small bowel even in previously inaccessible areas and anatomical configurations that result from surgical procedures such as a Roux-en-Y reconstruction with diagnostic and therapeutic endoscopic interventions rendered feasible and safe. In Roux-en-Y patients with a suspected stricture of a hepaticojejunostomy or suspected choledocholithiasis, DB-ERCP should strongly be considered. The value of the procedure could further be improved by expanding the currently limited availability of adapted accessories (20).

Endoscopic access via percutaneous access hepaticojejunostomy or endoscopic access hepatico-jejunostomy is effective for repeated access of the intrahepatic biliary system has been shown to improve results in patients with post anastomotic stricture or stone formation (21).

Balloon dilatation of a benign stricture is usually combined with stenting and rarely performed in isolation as its alone results in up to 47% restenosis. The main indication for balloon dilatation alone is in the setting



of Primary Sclerosing Cholangitis (PSC) with a dominant stricture. Insertion of a single plastic stent is rarely performed due to low patency rates; rather, several overlapping plastic stents are deployed over multiple sessions or a selfexpandable metal stents that are fully covered (FC-SEMS) in a membrane that prevents soft tissue hyperplasia, thus allowing for easier removal. These have mostly replaced the use of plastic stents due to their relative ease of removal, longer patency, and increased diameter. Bare metal stents are no longer used for benign strictures, as they may be irremovable due to embedment within the biliary epithelium (22).

SEMS stent therapy duration of 2 to 6 months has been commonly suggested with stricture resolution has ranged from 60% to 100% at the time of stent removal. Migration rates were variable between 10% and 40%. To solve this problem, partially covered SEMS (PC-SEMS) were used for benign biliary strictures (BBS) that are uncovered at both the proximal and distal ends of the stent that theoretically decrease the rate of stent migration but increase the risk of tissue embedment and difficulty in removing the stent **(23)**.

Endoscopic ultrasound (EUS) with or without endoscopic retrograde cholangiopancreatography (ERCP), has the benefit of allowing for tissue sampling with cytologic brushings or fine needle aspiration with or without further interventions including balloon angioplasty or stent insertion can also be performed concomitantly. Intraductal endoscopic ultrasound (IDUS) is a newer which utilizes technique а highfrequency, wire-guided ultrasound probe that is inserted into the extrahepatic bile ducts during ERCP. It has shown the

ability to diagnose biliary strictures caused by malignant tumors which were not visible on CT. The disadvantage of ERCP with IDUS/EUS is its requirement for an invasive endoscopic procedure with risks such as biliary or bowel perforation **(22)**.

### II) Radiological (percutaneous) management:

Percutaneous therapy is indicated in patients with strictures not amenable to endoscopic treatment especially patients with postsurgical anatomic variations of theproximal bowel or those with severe duodenal or papillary stenosis preventing CBD cannulation or postpyloric passage of the endoscope (22).

Percutaneous transhepatic management of benign biliary strictures involves repeated balloon dilatations with an indwelling catheter placed for the period of treatment. Now, being widely employed, a variable success rates have been reported in ductal (76% to 88%) and anastomotic strictures (67% to 73%). It is a minimally invasive approach that utilizes standard commonly used devices that are less expensive and definitely less morbid than a major open surgery requiring general anesthesia and intensive postoperative care. Irrespective of the underlying pathology balloon dilatation provides excellent relief from symptoms in patient with bilioenteric strictures (24).

It has the ability to precisely define the anatomy of the bile tree with percutaneous transhepatic cholangiography (PTC), locate the level of obstruction, and identify obstructing lesions or stones. PTC also enables direct access to the biliary tree, allowing for percutaneous decompression, balloon



dilatation, or stone removal. Balloon dilation of new surgical anastomoses can be potentially harmful and may lead to bile leak. Finally, short-segment strictures respond better to balloon dilation than long-segment ones, with short-term patency rates of 50 to 90% and long-term patency rates of 56 to 74%. Most benign strictures are amenable to balloon dilation (22).

An 8 to 10 mm-wide and 2 to 4 cmlong balloon is often used to dilate a proximal CBD or common hepatic duct stricture and larger balloons can be used, especially at the biliary-enteric anastomosis. The balloon is inflated for at least 1 minute and is usually reinflated several times. An internal-external locking catheter is then inserted with side holes both proximal and distal to the stenosis with sequential upsizing up to approximately 16F over multiple sessions every 3 to 6 weeks. Successful dilation will be evident on sheath cholangiography with evidence of prompt excretion of contrast without residual stenosis. Permanent indwelling of internal-external catheter may be required in patients who fail dilation therapy for drainage and must return every 3months for catheter exchange to prevent occlusion (22).

Unlike endoscopic management, stents (fully covered, self-expandable metallic stents) are generally only deployed percutaneously for resistant strictures with patency rate of 91% at 1 year (22).Self-expandable stents made of bioabsorbable material may have several advantages compared to the plastic and self-expandable metal stent because of improved patency for their larger diameter, lower biofilm accumulation, reduced bile duct proliferation changes and no need for stent removal. In addition, they can be impregnated with antimicrobial or anti-neoplastic agents. Larger studies are needed to demonstrate long-term efficacy and safety of biodegradable stents for a broad range of benign indications (23).

#### III) Surgical management:

isolated In patients with hepaticojejunostomy strictures, first-line treatment should be as much conservative as possible. Revisional surgery should remain a second-line treatment since the vast majority of strictures can be managed conservatively with well-conducted percutaneous or endoscopic dilatation as it represents a real therapeutic challenge requiring expertise in both liver and biliary surgery (25).

Surgery is performed in a context of chronic sepsis and after a long history of percutaneous maneuvers which encounters the fact that biliary strictures are often found at a higher level than during the first attempt (Figure 2).Operative identification of the anatomy and/or abnormalities may be difficult and requires systematic use of intraoperative cholangiography. Preoperative transhepatic cholangiography followed bv transhepatic biliary drainage should be left in place before surgery as it may be useful in localizing the bile duct after removal of the HJ and dissecting the hilar plate to expose the primary biliary confluence. In cases when the biliary confluence is not identifiable, а hepatotomy between segments 5 and 4 through of the bed of the gallbladder may be used to access the secondary right biliary confluence (19,26).





Figure (2): Management of HJ stricture (19).

Liver transplantation is a debatable option and only indicated in patients with irreversible parenchymal damage due to secondary biliary cirrhosis and chronic liver failure which should be only considered after failure of all therapeutic strategies and should remain exceptional (19).

Half of the patients present within 100 days after surgery, but the prevalence doubles long after liver transplantation. Risk factors for AS were postoperative bile leakage, a female donor/male recipient combination, and the era of transplantation. ERCP is a good primary modality of treatment, with high rates of success when the stenosis can be passed and dilatation and stenting can be performed**(26)**.

#### CONCLUSION:

Biliary-enteric anastomotic strictures occur with significant frequency after a biliary-enteric anastomosis. Although many patients are managed nonoperatively, stricture diagnosis remains burdensome.

The most challenging narrow stenosis to treat is one that develops years after transplantation. PTCD can be

used if ERCP is unsuccessful or if a primary hepaticojejunostomy is present.

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Surgery can always be used to treat anastomotic biliary stricture if nonoperative treatment is unsuccessful. Anastomotic biliary stricture with patients without AS, patients with AS had comparable rates of transplant and patient survival.

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### **REFERENCES:**

- Okabayashi, T., Shima, Y., Sumiyoshi, T., Sui, K., Iwata, J., Morita, S., ...& Shimada, Y. (2018). Incidence and risk factors of cholangitis after hepaticojejunostomy. Journal of Gastrointestinal Surgery, 22(4), 676-683.
- Tomoda, T., Tsutsumi, K., Kato, H., Mizukawa, S., Yabe, S., Akimoto, Y., ...& Okada, H. (2016). Outcomes of management for biliary stricture after



living donor liver transplantation with hepaticojejunostomy using short-type double-balloon enteroscopy. Surgical endoscopy, 30(12), 5338-5344.

- Kozicki, I., &Bielecki, K. (1997). Hepaticojejunostomy in Benign Biliary Stricture–Influence of Careful Postoperative Observations on Long-Term Results. Digestive Surgery, 14(6), 527-533.
- Liu, H., Shen, S., Wang, Y., & Liu, H. (2016). Biliary reconstruction and Roux-en-Y hepaticojejunostomy for the management of complicated biliary strictures after bile duct injury. International Surgery Journal, 2(2), 179-186.
- 5- Villa N. and Harrison M. (2015): Management of Biliary Strictures After Liver Transplantation. GastroenterolHepatol (N Y);11(5):316-28.
- 6- Moris D., Papalampros A., Vailas M., Petrou A., Kontos M., et al. (2016): The Hepaticojejunostomy Technique with Intra-Anastomotic Stent in Biliary Diseases and Its Evolution throughout the Years: A Technical Analysis. Gastroenterol Res Pract; 2016: 3692096.
- Fernández-Simon A., Díaz-Gonzalez A., Thuluvath P. and Cárdenas A. (2014):
  Endoscopic retrograde cholangiography for biliary anastomotic strictures after liver transplantation. Clin Liver Dis; 18(4):913-26.
- 8- Wang L. and Yu W. (2014): Obstructive jaundice and perioperative management. ActaAnaesthesiol Taiwan; 52(1):22-9.
- 9- Strasberg S. and Hawkins W. (2007): Reconstruction of the bile duct: Anatomic principles and surgical techniques. In: Mastery of surgery, 5th

ed. Philadelphia, Lippincott Williams and Wilkins, (pp.1128-1144).

- 10- Rösch T., Meining A., Frühmorgen S., Zillinger C., Schusdziarra V., et al. (2002): A prospective comparison of the diagnostic accuracy of ERCP, MRCP, CT, and EUS in biliary strictures. Gastrointest Endosc;55(7):870-6.
- **11-** Altman A. and Zangan S. (2016):Benignbiliarystrictures.SeminInterventRadiol; 33(4):297-306.
- 12- Gouma D. and Obertop H. (2002): Management of bile duct injuries: treatment and long-term results. Dig Surg;19(2):117-22.
- 13- Gupta V. and Jain G. (2019): Safe laparoscopic cholecystectomy: Adoption of universal culture of safety in cholecystectomy. World J GastrointestSurg; 27:11(2):62-84.
- Yeh B., Liu P., Soto J., Corvera C. and Hussain H. (2009): MR imaging and CT of the biliary tract. Radiographics;29(6):1669-88.
- 15- Quintero G. and Patiño J. (2001): Surgical management of benign strictures of the biliary tract. World J Surg; 25(10):1245–1250.
- 16- Dadhwal U. and Kumar V. (2012): Benign bile duct strictures. Med J Armed Forces India; 68(3):299-303.
- 17- Williams N., Bulstrode C. and O'Connell P. (2013): Dimethyl Iminodiacetic Acid (HIDA) Scan. In: Bailey And Love's Short Practice of Surgery, 26th Edition, CRC Press. New York.
- 18- Judah J. and Draganov P. (2007): Endoscopic therapy of benign biliary strictures. World J Gastroenterol;13(26):3531-9.
- 19- Cauchy F and Belghiti J (2015):"Hepaticojejunostomy Anastomotic Strictures". In: Gastrointestinal



Surgery. Springer, New York, pp. 239-248, Ch 23.

- 20- Koornstra J. (2008): Double balloon enteroscopy for endoscopic retrograde cholangiopancreaticography after Roux-en-Y reconstruction: case series and review of the literature. Neth J Med;66(7):275-9.
- 21- Prakash K., Ramesh H., Jacob G., Venugopal A., Lekha V., et al. (2004): Multidisciplinary approach in the longterm management of intrahepatic stones: Indian experience. Indian J Gastroenterol; 23(6):209-13.
- 22- Prieto M., Valdivieso A., Gastaca M., Pijoan J., Ruiz P., et al. (2019): Hepaticojejunostomy in Orthotopic Liver Transplant: A Retrospective Case Control Study. Transplant Proc; 51(1):58-61.
- 23- Tringali A. (2015): Endoscopic management of benign biliary strictures. Journal of Gastroenterology and Hepatology Research; 4(7): 1671-1683.
- 24- Kulkarni C., Pullara S., Moorthy S., Prabhu K., Kader N., et al. (2015): Percutaneous transhepatic balloon dilatation of benign bilioenteric strictures: Analysis of technique and long-term outcome. GastrointestInterv; 4 (2):112–119.
- **25-** Hamad M. and El-Amin H. (2012): Bilio-entero-gastrostomy: prospective assessment of a modified biliary reconstruction with facilitated future endoscopic access. BMC Surg; 12:9.
- 26- Verdonk, R. C., Buis, C. I., Porte, R. J., Van der Jagt, E. J., Limburg, A. J., Van den Berg, A. P., Haagsma, E. B. (2006). Anastomotic biliary strictures after liver transplantation: causes and consequences. Liver Transplantation, 12(5), 726-735.

