

# Management of biliary complications after orthotopic liver transplantation: The role of endoscopy

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## Abstract

Biliary complications are significant causes of morbidity and mortality after orthotopic liver transplantation (OLT). The estimated incidence of biliary complications after OLT ranges between 10%-25%, however, these numbers continue to decline due to improvement in surgical techniques. The most common biliary complications are strictures (both anastomotic and non-anastomotic) and bile leaks. Most of these problems can be appropriately managed with endoscopic retrograde cholangiography (ERC). Other complications such as bile duct stones, bile casts, sphincter of Oddi dysfunction, and hemobilia, are less frequent and also can be managed with ERC. This article will review the risk factors, diagnosis, and endoscopic management of the most common biliary complications after OLT.

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**Key words:** Endoscopic retrograde cholangiopancreatography; Orthotopic liver transplantation; Biliary strictures; Bile leaks

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## INTRODUCTION

Complications of the biliary tract after orthotopic liver transplantation (OLT) are an important cause of morbidity and mortality in liver transplant recipients. The most

frequent biliary complications following LT are biliary tract strictures, bile leaks, and bile duct stones. Biliary complications arising after a liver transplantation occur in 10% to 25% of cases, with biliary strictures, bile leaks, and bile duct stones accounting for the majority of the complications<sup>[1-6]</sup>.

These complications can be successfully managed with endoscopic retrograde cholangiography (ERC) in most cases. This article will review the different types of biliary complications after OLT and their endoscopic management.

## RISK FACTORS

Risk factors for the development of biliary complications after OLT are shown in Table 1. A major risk factor is the type of biliary reconstruction (duct-to-duct choledocho-choledochostomy *vs* Roux-en-Y choledochojejunostomy). The risk of biliary complications with the Roux en Y reconstruction is similar or only slightly higher compared with the duct-to-duct anastomosis<sup>[2,7-10]</sup>. Duct-to-duct anastomosis of the common bile duct has the advantage of including easy access to the biliary system after OLT and preservation of the sphincter of Oddi<sup>[11]</sup>. The use of T-tubes has also been implicated as a risk factor after OLT, although this issue is controversial. Some centers prefer the routine use of T-tubes for bridging of the biliary anastomosis as it allows the assessment of the quality and quantity of bile, biliary tract anatomy, and reduces the incidence of strictures. Despite these benefits, comparative studies indicate that routine T-tube placement is associated with higher incidence of bile leaks and cholangitis<sup>[12-15]</sup>.

Acute hepatic artery thrombosis, which may lead to ischemic strictures unless vascular flow is immediately reconstituted, is one of the major risk factors for the development of complications after OLT<sup>[12]</sup>. Other risk factors for the development of biliary complications include technical factors during surgery (excess dissection of periductal tissue during procurement and tension of the duct anastomosis), ischemia/reperfusion injury, cytomegalovirus infection, non-heart beating donors, ABO incompatibility and primary sclerosing cholangitis<sup>[12,16-22]</sup>.

## DIAGNOSIS

Patients may present with asymptomatic elevations of serum transaminases, serum bilirubin, alkaline phosphatase and/or  $\gamma$ -glutamyl transferase levels. In some cases patients may have non-specific symptoms, such as fever and anorexia<sup>[10,11,16]</sup>. In the initial evaluation of these

**Table 1 Risk factors for the development of biliary complications after OLT**

- 1 T-tube
- 2 Roux-en-Y anastomosis
- 3 Ischemia/Reperfusion injury
- 4 Acute hepatic artery thrombosis
- 5 Infections
- 6 ABO mismatch
- 7 Non-heart beating donors
- 8 Primary sclerosis cholangitis

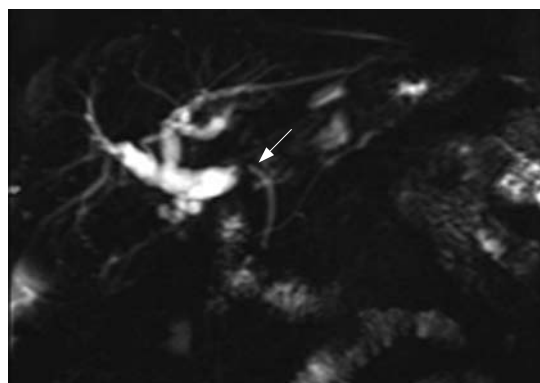
patients, an abdominal/liver ultrasound (US) should be performed to evaluate the biliary tree and the hepatic vessels. If hepatic artery stenosis is suspected, a hepatic angiography is usually indicated. Liver biopsy is useful in order to exclude rejection, but histological features of biliary obstruction can sometimes be misleading and confused with rejection or hepatitis C recurrence<sup>[23]</sup>. In cases where there is biliary dilation on the abdominal US, liver biopsy is not initially performed due to the risk of causing a bile leak. The yield of abdominal US in detecting biliary complications is sometimes limited by a lack of good sensitivity and accuracy to detect common bile duct obstruction or stones. Hence, the absence of bile duct dilation on US should not preclude further evaluation with other sensitive techniques (see below) in patients in whom there is suspicion of biliary tract complications.

If there is a strong clinical suspicion of bile duct obstruction or bile leak, a cholangiogram, by means of endoscopy or radiology, should always be performed. In recent years, the role of magnetic resonance cholangiopancreatography (MRCP) as a tool to evaluate the biliary tract of post-OLT patients has significantly improved. Recent studies demonstrate that MRCP has high sensitivity and specificity in detecting biliary complications after OLT (93%-100% and 92%-98%, respectively). MRCP is particularly useful in patients with a low suspicion of biliary complications or when there is a low probability of ERC or percutaneous transhepatic cholangiography (PTC)<sup>[24,25]</sup> (Figure 1). In patients with an indwelling T-tube, a T-tube cholangiography is the method of choice to evaluate the biliary tract. The best diagnostic approach (ERC *vs* PTC) depends on the type of biliary reconstruction, the likelihood of therapeutic intervention, and the center's expertise. ERC is probably the best diagnostic intervention in patients with duct-to-duct anastomosis, while PTC should be performed in cases of failed ERC or in patients with a Roux-en-Y anastomosis. In high volume centers with experienced endoscopists, ERC can be successfully performed with a variable stiffness pediatric colonoscope. In one report from the Mayo Clinic, 22 out of 31 patients post-OLT with Roux-en-Y anastomosis referred for ERC were successfully treated with endoscopy<sup>[26]</sup>.

## MANAGEMENT

### Strictures

Bile duct strictures are the most common biliary complication after OLT with an incidence ranging between 4% and 16%<sup>[1-6,10,11,16,27-30]</sup>. Strictures are divided into



**Figure 1** Magnetic resonance cholangiopancreatography (MRCP) image of the biliary tract of a patient that developed abnormal liver enzymes 8 mo after liver transplantation. The MRCP showed a severe biliary stricture at the anastomotic site (arrow).



**Figure 2** Endoscopic retrograde cholangiography (ERC) in a patient that developed pruritus and cholestasis 6 mo after liver transplantation. The ERC showed a severe anastomosis stricture (arrow). This stricture was successfully managed with biliary balloon dilation and stent placement.

early (within 1 mo of OLT, usually related to technical problems) and late strictures (after 1 mo of OLT, mainly secondary to vascular insufficiency). In addition, bile duct strictures are classified as anastomotic (AS) or non-anastomotic (NAS) depending on the stricture site<sup>[16]</sup>.

In some patients, within the first two months after surgery, a narrowing of the anastomosis (mainly due to postoperative edema and inflammation) may occur and in general responds to one session of endoscopic biliary balloon dilation (6-8 mm) and plastic stent placement (7 French) with removal 6-8 wk later<sup>[10]</sup>. The majority of true AS occur between the first 3 and 12 mo after OLT (Figure 2). The preferred endoscopic treatment for AS is the repeated combination of biliary balloon dilation (6-10 mm) plus the use of plastic stents ranging from 7-11.5 F with increasing diameter and number, if possible<sup>[30-33]</sup>. These strictures often recur (recurrence rate of 30%-40%) and in many cases require long-term stenting (up to 24 mo)<sup>[31]</sup>. The efficacy of this combined approach has been confirmed in at least two studies. In one study of 24 patients, combination treatment of biliary balloon dilatation and stent placement was more effective than balloon dilation alone (success rate of 88% *vs* 37.5%, respectively)<sup>[32]</sup>. In another study, 22 patients with AS

**Table 2** Key points in the management of bile duct strictures

- Bile duct strictures can be classified as anastomotic or non-anastomotic
- Early anastomotic strictures usually respond to endoscopic dilation and short-term stenting
- Late anastomotic strictures have a high rate of recurrence (30%-40%) requiring long-term stenting (up to 24 mo).
- If endoscopic or percutaneous treatment fails, surgical repair or conversion to Roux-en-Y choledochojejunostomy may be necessary
- Non-anastomotic strictures require long-term stenting
- Some patients do not respond and finally undergo re-transplantation or die because of this complication

underwent endoscopic dilation plus maximal stenting [up to 4 stents (range 7-11.5 French)] and in 81% cases complete resolution of the stenosis was achieved in a mean period of 4.6 mo<sup>[33]</sup>. It is recommended that plastic stents be exchanged every 3-mo to avoid stent occlusion. With this approach 67%-91% of patients respond to endoscopic treatment alone<sup>[3,29,30,32,33]</sup>. In patients with Roux-en-Y anastomosis, PTC and dilation followed by placement of a percutaneous transhepatic catheter are recommended. If endoscopic or percutaneous therapy fails, surgical repair or conversion to a Roux-en-Y anastomosis may be necessary for successful long-term outcome.

NAS are mainly due to vascular problems and ischemia. Recurrence of primary sclerosing cholangitis is also a cause of NAS. The incidence of NAS ranges between 0.5% and 9.6%<sup>[2,6,8,28,29,34,35]</sup>. These strictures tend to occur earlier than AS (3-6 mo after OLT)<sup>[29,34]</sup>. Endoscopic treatment of NAS is similar to that for AS, and typically consists of 4-6 mm biliary balloon dilation (compared to 6-10 mm for AS) and placement of plastic stents<sup>[29]</sup>. The time to response is longer in NAS compared to AS. In one study, the median time to response was 185 d for NAS compared to 67 d for AS<sup>[35]</sup>. Despite endoscopic treatment with biliary balloon dilation and stenting, nearly 30%-50% of patients undergo re-transplantation or have a fatal outcome as a consequence of NAS<sup>[11,16,29,34,36]</sup>. The key features in the management of bile duct strictures post-OLT are described in Table 2.

### Bile leaks

Bile leaks are a common complication after OLT with an incidence ranging between 2%-25%<sup>[1-6,16,27,37]</sup>. Leakage may arise from the anastomosis, the cystic duct, or T-tube (Figure 3). Bile leaks can also be divided into early (within 4 wk after transplantation) and late<sup>[16]</sup>. Early bile leaks usually arise from the anastomosis and are related to technical problems, such as insufficient blood flow from the hepatic artery to the anastomosis and other factors described in Table 1. Patients with bile leaks may be asymptomatic (bile leak detected by the presence of fluid collection on abdominal ultrasound or CT scan) or present with a clinical picture of peritonitis. In patients with a T-tube in place, bile leaks may be detected with a T-tube cholangiogram and managed by leaving the tube open without further intervention<sup>[16]</sup>. In patients without a T-tube, ERC is the preferred diagnostic test. In addition, ERC with biliary sphincterotomy and stent placement is the method of choice to treat bile leaks (success rate



**Figure 3** Endoscopic retrograde cholangiography (ERC) image of a biliary leak in a patient after a liver transplantation. The arrow is pointing to the area of extravasation of contrast from the biliary tree.

of 95%)<sup>[4,5,38,39]</sup>. In these patients, the stent is left in place for 2-3 mo<sup>[16]</sup>. Small leaks can be managed with biliary sphincterotomy alone<sup>[40]</sup>. In patients with Roux-en-Y anastomosis, bile leaks can be managed with percutaneous internal-external drainage, however, they often require surgical management. Late bile leaks are commonly related to the removal of the T-tube because the tract is often not mature due to immunosuppressive therapy. Patients that complain of abdominal pain after T-tube removal should raise the concern for a bile leak. In these cases, symptoms resolve with analgesia without further intervention<sup>[1-6,16,37,41]</sup>.

## OTHER COMPLICATIONS

### Biloma

Bilomas occur due to bile rupture and extravasation of bile within the liver or the abdominal cavity. If the biloma communicates with the biliary tree, it may resolve spontaneously or occasionally with the placement of a plastic stent in the extrahepatic bile duct. Large bilomas not communicating with the bile ducts should be treated with percutaneous drainage along with antibiotics. If bile leaks cannot be effectively controlled with the abovementioned treatments, surgery is indicated.

### Common bile duct filling defects

Most filling defects are caused by gallstones<sup>[5]</sup>. Other causes include sludge, blood clots, casts and migrated stents. Biliary stones and sludge are relatively common after OLT, with an incidence between 3% and 12%<sup>[3-5,8,42]</sup>. Factors related to the formation of stones and sludge are the presence of strictures, bacterial infection and obstruction<sup>[10,16,27]</sup>. In many cases (66%), one session of ERC with sphincterotomy stone extraction is adequate to clear the duct<sup>[5]</sup>. Bile casts are seen in the setting of ischemia. Clearance of casts may be difficult to achieve with endoscopic methods. Various combinations of sphincterotomy, balloon and basket extraction, stent placement and lithotripsy are often necessary and many of these patients require management with PTC<sup>[43]</sup>.

### Sphincter of Oddi dysfunction

It has been postulated that denervation of the common bile duct in the ampullary region secondary to surgical



intervention may lead to the development of a hypertonic sphincter causing sphincter of Oddi dysfunction<sup>[11,27]</sup>. Endoscopy therapy with biliary sphincterotomy is the treatment of choice in cases of a uniformly dilated common bile duct with cholestasis without any other obvious cause for abnormal liver chemistries.

### Mucocele

A mucocele is a rare complication after OLT caused by a collection of mucus from the cells lining the cystic duct remnant. The diagnosis can be confirmed with MRCP. Patients usually require surgical or radiological drainage<sup>[16,44]</sup>.

## CONCLUSION

Biliary complications arising after OLT occur in approximately 10%-25% of cases. Biliary strictures, bile leaks and bile duct stones account for the majority of these complications. The diagnostic approach of biliary complications after OLT should begin with a liver US and Doppler examination of the hepatic artery. In cases with a strong clinical and radiological suspicion of biliary pathology, the patient should proceed directly to ERC. MRCP is an excellent diagnostic tool for the evaluation of the biliary tree after OLT and should be performed in cases where there is a lower suspicion for biliary pathology. Patients with AS and NAS should undergo repeated ERC sessions with biliary balloon dilatation and placement of plastic stents to achieve maximal diameter with routine stent changes every 3 mo. In most cases, patients require between 3 and 5 sessions. In patients with bile leaks, ERC with or without sphincterotomy with placement of a plastic stent, which should be left in place for 2-3 mo, is recommended. Other complications such as common bile duct stones, casts, mucocele or sphincter of Oddi dysfunction can be managed successfully with ERC and standard techniques for removal of stones and sphincterotomy.

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