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.

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 choledochocholedochostomy 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.[2,7-10]. 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.[11]. 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.[12-15].

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.[16]. 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.[12,16-22].

DIAGNOSIS

Patients may present with asymptomatic elevations of serum transaminases, serum bilirubin, alkaline phosphatase and/or y-glutamyl transferase levels. In some cases patients may have non-specific symptoms, such as fever and anorexia.[10,11,16]. In the initial evaluation of these
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[23]. 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)[24,25] (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[26].

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 sclerosing cholangitis |

MANAGEMENT

Strictures

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

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[10]. 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[30-33]. These strictures often recur (recurrence rate of 30%-40%) and in many cases require long-term stenting (up to 24 mo)[30]. 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)[32]. In another study, 22 patients with AS
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\(^2\). 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\(^3\). 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%\(^4\). These strictures tend to occur earlier than AS (3-6 mo after OLT)\(^5\). 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\(^6\). 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\(^7\). 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\(^8\). The key features in the management of bile duct strictures post-OLT are described in Table 2.

**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 cholecystojunostomy 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

Bile leaks

Bile leaks are a common complication after OLT with an incidence ranging between 2%-25%\(^9\). Leakage may arise from the anastomosis and are related to technical problems, such as insufficient blood flow from the hepatic artery to the anastomosis and are related to the formation of stones and sludge. Factors related to the formation of stones and sludge are the presence of strictures, bacterial infection and obstruction\(^10\). In many cases (66%), one session of ERC with sphincterotomy stone extraction is adequate to clear the duct\(^11\). Bile leaks cannot be effectively controlled with the aforementioned treatments, surgery is indicated.

**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 biliary 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\(^1\). 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%\(^2\). Factors related to the formation of stones and sludge are the presence of strictures, bacterial infection and obstruction\(^10\). In many cases (66%), one session of ERC with sphincterotomy stone extraction is adequate to clear the duct\(^11\). 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\(^12\).

**Sphincter of Oddi dysfunction**

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

- **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.**

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intervention may lead to the development of a hypertonic sphincter causing sphincter of Oddi dysfunction.\textsuperscript{11,27} 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.\textsuperscript{13,14}

**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.

**REFERENCES**

1. Stratta RJ, Wood RP, Langnas AN, Hollins RR, Bruder KJ, Donovan JP, Burnett DA, Lieberman RP, Lund GB, Pillen TJ. Diagnosis and treatment of biliary tract complications after orthotopic liver transplantation. Surgery 1989; 106: 675-683; discussion 683-684
2. Greff F, Bronsther OL, Van Thiel DH, Casavilla A, Iwatsuki S, Tazakis A, Todo S, Fung JJ, Starzl TE. The incidence, timing, and management of biliary tract complications after orthotopic liver transplantation. Ann Surg 1994; 219: 40-45
3. Rerknimitr R, Sherman S, Fogel EL, Kalayci C, Lumeng L, Chalasani N, Kwo P, Lehman GA. Biliary tract complications after orthotopic liver transplantation with choledochocholedochostomy anastomosis: endoscopic findings and results of therapy. Gastrointest Endosc 2002; 55: 224-231
4. Pfau PR, Kochman ML, Lewis JD, Long WB, Lucey MR, OIthoff K, Shaked A, Ginsberg GG. Endoscopic management of postoperative biliary complications in orthotopic liver transplantation. Gastrointest Endosc 2000; 52: 55-63
5. Thuluvath PJ, Atassi T, Lee J. An endoscopic approach to biliary complications following orthotopic liver transplantation. Liver Int 2003; 23: 156-162
6. Thethy S, Thomson BNj, Pleass H, Wigmore SJ, Madhavan K, Akyol M, Fosythe JL. James Garden O. Management of biliary tract complications after orthotopic liver transplantation. Clin Transplant 2004; 18: 647-653
7. Davidson BR, Rai R, Kupciwski TR, Selves L, Farouk M, Dooley JS, Burroughs AK, Rolles K. Prospective randomized trial of end-to-end versus side-to-side biliary reconnection after orthotopic liver transplantation. Br J Surg 1999; 86: 447-452
8. Park JS, Kim MH, Lee SK, Seo DW, Lee SS, Han J, Min YJ, Hwang S, Park KM, Lee YJ, Lee SG, Sung KB. Efficacy of endoscopic and percutaneous treatments for biliary complications after cadaveric and living donor liver transplantation. Gastrointest Endosc 2003; 57: 78-85
9. Sawyer RG, Punch JD. Incidence and management of biliary complications after 291 liver transplants following the introduction of transcystic stenting. Transplantation 1998; 66: 1201-1207
10. Verdonk RC, Buis CI, Porte RJ, Haagsma EB. Biliary complications after liver transplantation: a review. Scand J Gastroenterol Suppl 2006: 89-101
11. Pascher A, Neuhaus P. Biliary complications after deceased-donor orthotopic liver transplantation. J Hepatobiliary Pancreat Surg 2006; 13: 487-496
12. Scallion O, Meunier B, Cherqui D, Boillot O, Sauvanet A, Boudjema K, Launois B, Fagniez PL, Belghiti J, Wolff P, Houssin D, Soubrane O. Randomized trial of choledochocholedochostomy with or without a T tube in orthotopic liver transplantation. Ann Surg 2001; 233: 432-437
13. Vougas V, Rela M, Gane E, Muiesan P, Melendez HV, Williams R, Heaton ND. A prospective randomised trial of bile duct reconstruction at liver transplantation: T tube or no T tube? Transpl Int 1996; 9: 392-395
14. Amador A, Charco R, Marti J, Alvarez G, Ferrer J, Mans E, Fuster J, Fondevilla C, Garcia-Valdecasas JC. Cost/efficacy clinical trial about the use of T-tube in cadaveric donor liver transplant: preliminary results. Transplant Proc 2005; 37: 1129-1130
15. Koivusalo A, Isoniemi H, Salmela K, Edgren J, von Numers Thethy S, Transplant Proc 2003; 35: 487-496
16. Sanchez-Urdazpal L, Gores GJ, Ward EM, Maus TP, Wahlstrom HE, Moore SB, Wiesner RH, Krom RA. Ischemic-type biliary complications after orthotopic liver transplantation. Hepatology 1992; 16: 49-53
17. Sanchez-Urdazpal L, Gores GJ, Ward EM, Maus TP, Buckel EG, Steers JL, Wiesner RH, Krom RA. Diagnostic features and clinical outcome of ischemic-type biliary complications after liver transplantation. Hepatology 1993; 17: 605-609
18. Busquets J, Figueras J, Serrano T, Torras J, Ramos E, Rafca A, Fabregat J, Lama C, Xiol X, Ballellas C, Jaurrieta E. Postreperfusion biopsies are useful in predicting complications after liver transplantation. Liver Transpl 2001; 7: 432-435
19. Sanchez-Urdazpal L, Batt PK, Gores GJ, Moore SB, Sterioff S, Wiesner RH, Krom RA. Increased bile duct complications in liver transplantation across the ABO barrier. Ann Surg 1993; 218: 152-158
20. Ludwig J, Wiesner RH, Batt PK, Perkins JD, Krom RA. The acute vanishing bile duct syndrome (acute irreversible rejection) after orthotopic liver transplantation. Ann Surg 2002; 236: 476-483
21. Graziaidei IW. Recurrence of primary sclerosing cholangitis after liver transplantation. Liver Transpl 2002; 8: 575-581
22. Scheuer P, Lefkowitz JH. The liver in organ transplantation. In: Liver biopsy interpretation. WB Saunders 2000: 323-343
23. Beltran MM, Marugan RB, Oton E, Blesa C, Nuno J. Accuracy of magnetic resonance cholangiography in the evaluation of late biliary complications after orthotopic liver transplantation. Transplant Proc 2005; 37: 3924-3925
24. Kitazono MT, Qayyum A, Yeh BM, Chard PS, Ostroff JW, Coalkey FV. Magnetic resonance cholangiography of biliary
strictures after liver transplantation: a prospective double-blind study. J Magn Reson Imaging 2007; 25: 1168-1173

26 Chahal P, Baron TH, Poterucha JJ, Rosen CB. Endoscopic retrograde cholangiography in post-orthotopic liver transplant population with Roux-en-Y biliary reconstruction. Liver Transpl 2007; 13: 1168-1173

27 Scanga AE, Kowdley KV. Management of biliary complications following orthotopic liver transplantation. Curr Gastroenterol Rep 2007; 9: 31-38

28 Koneru B, Sterling MJ, Bahramipour PF. Bile duct strictures after liver transplantation: a changing landscape of the Achilles' heel. Liver Transpl 2006; 12: 702-704

29 Grazia dei IW, Schweighofer H, Koch R, Nachbaur K, Koenigsrainer A, Margreiter R, Vogel W. Long-term outcome of endoscopic treatment of biliary strictures after liver transplantation. Liver Transpl 2006; 12: 718-725

30 Verdonk RC, Buis CI, Porte RJ, van der Jagt EJ, Limburg AJ, van den Berg AP, Sloop MJ, Peeters PM, de Jong KP, Kleibeuker JH, Haagsma EB. Anastomotic biliary strictures after liver transplantation: causes and consequences. Liver Transpl 2006; 12: 726-735

31 Alazmi WM, Fogel EL, Watkins JL, McHenry L, Tector JA, Fridell J, Mosler P, Sherman S, Lehman GA. Recurrence rate of anastomotic biliary strictures in patients who have had previous successful endoscopic therapy for anastomotic narrowing after orthotopic liver transplantation. Endoscopy 2006; 38: 571-574

32 Zoepf T, Maldonado-Lopez EJ, Hilgard P, Malago M, Broelsch CE, Treichel U, Gerken G. Balloon dilatation vs. balloon dilatation plus bile duct endoprostheses for treatment of anastomotic biliary strictures after liver transplantation. Liver Transpl 2006; 12: 88-94

33 Pasha SF, Harrison ME, Das A, Nguyen CC, Vargas HE, Balan V, Byrne TJ, Douglas DD, Mulligan DC. Endoscopic treatment of anastomotic biliary strictures after deceased donor liver transplantation: outcomes after maximal stent therapy. Gastrointest Endosc 2007; 66: 44-51

34 Guichelaar MM, Benson JT, Malinchoc M, Krom RA, Wiesner RH, Charlton MR. Risk factors for and clinical course of non-anastomotic biliary strictures after liver transplantation. Am J Transplant 2003; 3: 885-890

35 Rizk RS, McVicar JP, Emond MJ, Rohrmann CA Jr, Kowdley KV, Perkins J, Carithers RL Jr, Kimney MB. Endoscopic management of biliary strictures in liver transplant recipients: effect on patient and graft survival. Gastrointest Endosc 1998; 47: 128-135

36 Verdonk RC, Buis CI, van der Jagt EJ, Gouw AS, Limburg AJ, Sloop MJ, Kleibeuker JH, Porte RJ, Haagsma EB. Nonanastomotic biliary strictures after liver transplantation, part 2: Management, outcome, and risk factors for disease progression. Liver Transpl 2007; 13: 725-732

37 Sheng R, Sammon JK, Zajko AB, Campbell WL. Bile leak after hepatic transplantation: cholangiographic features, prevalence, and clinical outcome. Radiology 1994; 192: 412-416

38 Morelli J, Mulcahy HE, Willner IR, Baliga P, Chavin KD, Patel R, Payne M, Cotton PB, Hawes R, Reuben A, Cunningham JT. Endoscopic treatment of post-liver transplantation biliary leaks with stent placement across the leak site. Gastrointest Endosc 2001; 54: 471-475

39 Sherman S, Shaked A, Cryer HM, Goldstein LI, Busuttil RW. Endoscopic management of biliary fistulas complicating liver transplantation and other hepatobiliary operations. Ann Surg 1993; 218: 167-175

40 Llach J, Bordas JM, Elizalde JI, Enrico C, Gines A, Pellise M, Mondelo F, Pique JM. Splinterhotroctominy in the treatment of biliary leakage. Hepatogastroenterology 2002; 49: 1496-1498

41 Saab S, Martin P, Soliman GM, Machadioca GA, Roth BE, Kunder G, Han SH, Farmer DG, Ghobrial RM, Busuttil RW, Bedford RA. Endoscopic management of biliary leaks after T-tube removal in liver transplant recipients: nasobiliary drainage versus biliary stenting. Liver Transpl 2000; 6: 627-632

42 Sheng R, Ramirez CB, Zajko AB, Campbell WL. Biliary stones and sludge in liver transplant patients: a 13-year experience. Radiology 1996; 198: 243-247

43 Shah JN, Haigh WG, Lee SP, Lucey MR, Brensinger CM, Kochman ML, Long WB, Othoff K, Shaked A, Ginsberg GG. Biliary casts after orthotopic liver transplantation: clinical factors, treatment, biochemical analysis. Am J Gastroenterol 2003; 98: 1861-1867

44 Zajko AB, Bennett MJ, Campbell WL, Koneru B. Mucocoele of the cystic duct remnant in eight liver transplant recipients: findings at cholangiography, CT, and US. Radiology 1990; 177: 691-693

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