



A Review on the Management of Biliary Complications after Orthotopic Liver Transplantation

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Abstract

Orthotopic liver transplantation is the definitive treatment for end-stage liver disease and hepatocellular carcinomas. Biliary complications are the most common complications seen after transplantation, with an incidence of 10–25%. These complications are seen both in deceased donor liver transplant and living donor liver transplant. Endoscopic treatment of biliary complications with endoscopic retrograde cholangiopancreatography (commonly known as ERCP) has become a mainstay in the management post-transplantation. The success rate has reached 80% in an experienced endoscopist's hands. If unsuccessful with ERCP, percutaneous transhepatic cholangiography can be an alternative therapy. Early recognition and treatment has been shown to improve morbidity and mortality in post-liver transplant patients. The focus of this review will be a learned discussion on the types, diagnosis, and treatment of biliary complications post-orthotopic liver transplantation.

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Introduction

Biliary tract complications are often seen in liver transplantation recipients and account for a major cause of morbidity and mortality in post-transplant patients. Common complications are anastomotic strictures (AnS), non-anastomotic strictures (NAnS), bile leaks, bile duct stones, bile casts, bilomas, mucocoeles, and hemobilia (Table 1).^{1–4} Bile duct complications often depend upon the type of transplant performed, either deceased donor or living donor liver transplant (DDLT and LDLT, respectively), the number of bile ducts involved,

Keywords: Biliary tract complication; Orthotopic liver transplantation; Stricture; Bile leak.

Abbreviations: AnS, anastomotic strictures; CBD, common bile duct; DDLT, deceased donor liver transplant; ERCP, endoscopic retrograde cholangiopancreatography; fcSEMS, fully covered self-expanding metal stent; LDLT, living donor liver transplant; MRCP, magnetic resonance cholangiopancreatography; NAnS, non-anastomotic strictures; OLT, orthotopic liver transplantation; PTC, percutaneous transhepatic cholangiography; SEMS, self-expanding metal stent; US, ultrasound.

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and the anastomosis chosen by the surgeon (choledochocholedochotomy or hepaticojejunostomy).¹

Early identification and quick treatment of recognized biliary complications following transplant have been shown to reduce morbidity and mortality, and to improve graft survival.¹ Overall, endoscopic retrograde cholangiopancreatography (ERCP) therapy is safe post-liver transplant and has a high success rate. ERCP complication rates of 5–9% post-orthotopic liver transplantation (OLT) are similar to non-transplant ERCP.^{5–9} There is an estimated 2-times to 3-times increased incidence of biliary complications in LDLT compared to DDLT.

Biliary complications can be organized as early (within 4 weeks) or late (after 4 weeks), and this should frame the practitioner's thinking (Table 2). However, since biliary complications based on timelines can be ambiguous, we based this review on occurrence frequency. The aim of this review is to go through how to recognize, diagnose, and treat biliary complications post-OLT with the most up-to-date research.

Biliary strictures

Forty percent of post-transplant biliary complications are from bile duct strictures.¹⁰ AnS account for 80% of all strictures, and NAnS account for about 20%.¹⁰ AnS are more commonly seen after LDLT than DDLT because LDLT anastomoses are made between multiple small peripheral bile ducts.¹ AnS that occur early after OLT are often due to surgical issues, whereas late AnS could be from primary ischemia with poor healing.^{11,12}

It is generally accepted that strictures of all types are more prevalent with Roux-en-Y choledochojejunostomy, but some contest this.^{4,13} Long-term biliary complications between duct-to-duct and Roux-en-Y surgeries are comparable in review of the literature.^{4,14–17} Grief *et al.*⁴ showed a higher incidence of post-transplant strictures with Roux-en-Y choledochojejunostomy. However, 1 year after transplant, the incidence of biliary strictures decreases to around 4%.¹⁸ There is also an increased risk for bile leaks if an AnS is present due to increases in biliary pressure.^{19,20}

AnS usually occur in the first 12 months, and are single, shorter, and within 5 mm of the anastomotic site.¹ The pathophysiological events can be multifactorial, such as inadequate mucosa at an anastomotic site, local tissue ischemia, localized edema, and fibrosis occurring at the site of healing.^{3,5,14} Early identification of the stricture correlates with a better response to short-term stenting (3–6 months).²¹ AnS within 3 months of transplant have been shown to have the best prognosis.²² After 12 months, AnS have a poorer response to stent and dilatation while relapse rate is high, at 30–40%.²²

Table 1. Biliary Complications after liver transplantation⁹³

Biliary complication	Risk factor	Incidence after liver transplantation
Anastomotic stricture	Ischemia, reperfusion injury, duct-to-duct anastomosis, and type of transplant	6–12%
Non-anastomotic stricture	Hepatic artery thrombosis, cold ischemia time	0.5–10%
Biloma	Hepatic artery ischemia, bile duct necrosis, ruptured bile duct	2.6–11.5%
Bile leak	Anastomosis type, PTC tube tract, excessive use of electrocautery, cut of liver intraoperatively	8%
Stones, sludge, clots	Stricture, ischemia, infections	5%
Biliary cast syndrome	Hepatic artery stenosis and stricture	2.5–3%
Hemobilia	PTC or biopsy	1%
Mucocele	Presence of mucous cells in cystic duct remnant	Rare

Abbreviation: PTC, percutaneous transhepatic cholangiography.

Diagnosis of anastomotic strictures

Biliary complications are often diagnosed in asymptomatic OLT recipients based on elevated liver function markers, including: aspartate aminotransferase/alanine aminotransferase, alkaline phosphatase, and gamma-glutamyltransferase. Clinically, patients may present with signs of cholangitis, including: fever, abdominal pain, jaundice, and confusion. The initial evaluation should include liver function tests and an ultrasound (US) with Doppler. These tests will help to evaluate the vasculature, to rule-out hepatic artery thrombosis.

Although a rare cause for biliary strictures, hepatic artery thrombosis is an emergency situation post-OLT and often results in graft failure. Hepatic artery thrombosis can be detected on US with Doppler, with a sensitivity of 91% and specificity of 99%.²³ If vascular obstruction is suspected on Doppler US, hepatic angiography can be considered to confirm the findings. US is also used in evaluation for biliary obstruction, with a sensitivity of 38–66%.^{18,24} The absence of bile duct dilation should not prevent further investigation if suspicion is high for biliary tract complication.

If the suspicion is high for biliary tract complication, along with an US that shows bile duct obstruction, a cholangiogram by ERCP or percutaneous transhepatic cholangiography (PTC) should be the next step (see below for magnetic resonance cholangiopancreatography (MRCP) utility in this evaluation).^{3,5,6,25–28} Liver biopsy can often reveal impaired bile flow suggestive of a biliary complication, but it is not always

apparent. Furthermore, liver biopsy can be performed in the acute setting to rule-out rejection or recurrence of hepatitis C.

In recent years, MRCP has gained more acceptance given the non-invasive nature of the technique and its ability to map out the biliary anatomy. MRCP has a sensitivity of 93–96% and specificity of 90–94% for diagnosing biliary obstruction.^{12,29} An MRCP is a good non-invasive alternative option for further investigation of the biliary tree when there is lower suspicion for a biliary complication. Its main disadvantage is the low sensitivity when looking for leaks, sludge, or small stones (<5 mm).³⁰

The decision to proceed with ERCP or PTC often depends on the biliary surgery performed at time of transplant. In patients with duct-to duct anastomosis, ERCP has been shown to be the test of choice when diagnosing and providing an intervention for a biliary complication.¹⁴ PTC is used when ERCP has been unsuccessful or in patients with Roux-en-Y choledochojejunostomy. In the subset of patients with a Roux-en-Y surgery, ERCP can be attempted using a balloon enteroscopy or with surgical assistance to access the small bowel for cannulation. If either PTC or ERCP can only provide diagnostic information but are therapeutically unsuccessful, Roux-en-Y choledochojejunostomy is a rescue surgical technique, with a 5-year survival rate at approximately 70%.^{5,11}

It is important to have an understanding of the different types of reconstruction that occur during OLT when evaluating a patient with a potential biliary complication. An end-to-end choledococholedocal anastomosis is the preferred surgery at most institutions.⁴ This method preserves the sphincter of Oddi and the connection between the biliary and enteral system, thus allowing access if needed with ERCP. Roux-en-Y is the other alternative surgery performed if there is underlying biliary disease, like in primary sclerosing cholangitis or if the bile ducts differ in size.²⁹ With LDLT, the living donor's right or left lobe is transplanted, which makes intra-hepatic ductal anastomosis more difficult to achieve because of the nature of the small caliber ducts.³⁰

Other than surgery type, risk factors for strictures include bile leak, hepatic artery thrombosis, hepatic artery stenosis, dissection of periductal tissue during procurement, use of electrocautery for biliary duct bleeding, and tension of the duct anastomosis. In an attempt to better hold the primary biliary anastomosis, a surgeon may use non-absorbable

Table 2. Timing of biliary complications after liver transplantation

Early complications (<4 weeks)	Late complications (>4 weeks)
Hemobilia, bile leaks, biloma	Biliary clots, biliary cast syndrome, stones, and sludge
Anastomosis necrosis and anastomotic stricture	Anastomotic and non-anastomotic stricture
Roux-en-Y torsion	Redundant common bile duct, mucocele

sutures. These sutures can then form a focus, called a surgical knot. The surgical knot can obstruct or migrate into the lumen, causing biliary complications. Additional risks for anastomotic strictures include different duct sizes between donor and recipient, ischemic injury, ABO incompatibility, cytomegalovirus infection, cold and warm ischemia times, recipient's and donor's age, prior liver dysfunction in the recipient, donation after cardiac death, and primary sclerosing cholangitis, and all can contribute to an AnS biliary stricture.^{5,12,15-18,28,31-38}

A T-tube is often placed across the biliary anastomosis during surgery, with the long limb of the "T" draining externally and allowing the flow of bile both into the intestine and into the drain after surgery.³⁹ Placement of a T-tube post-liver transplant is associated with a higher incidence of biliary complications, such as strictures, bile leaks, and cholangitis.^{19,40-43} A meta-analysis looking at six randomized controlled trials showed no benefit with T-tube placement.²⁰ T-tube placement for duct reconstruction in DDLT patients has shown a decreased incidence of AnS; however, this feature has come at the cost of an increased risk for biliary leakage after removal of the T-tube, which is reported to be 5-33%.⁴⁴ One advantage of the T-tube is the ability to perform direct cholangiography easily with the tube in place.³⁹ T tube-placement in liver transplant is controversial and more studies need to be done on its efficacy overall and in specific situations.

Management of AnS

The mainstay of anastomotic stricture management revolves around ERCP therapy. Most patients will require multiple ERCP sessions every 3 months, with stenting and dilation for 1-2 years. Typically, a guidewire is placed across the stricture, dilated with 6-8 mm balloons and then one or multiple 7 to 11.5 Fr plastic stents are placed. Historically, some endoscopists have proceeded with dilation alone, which has been shown to be less effective than combined dilation with periodic stenting.^{1,3,18,23} In a head-to-head study, combination therapy was more effective than balloon dilation alone in 24 patients.^{45,46} In another retrospective study, dilate/stent therapy was also more effective than balloon dilation alone (88% vs. 37%).⁴⁵ In a systematic review by Kao *et al.*⁴⁷, the average number of ERCP sessions for AnS is 2.7 to 5.4, with placement of 1.9 to 2.5 stents with each ERCP.

Plastic stents should be exchanged every 3 months to avoid occlusion causing cholangitis. In a review of 440 transplanted patients with AnS treated by plastic stents during ERCP, the resolution rate was 85%. Rate of recurrence depended on duration of stenting. Less than 12 months of stenting had a 78% stricture resolution rate, while >12 months had a 97% resolution rate.⁴⁷ Tabibian *et al.*⁴⁸ looked at 83 patients with AnS 20 months after OLT. Sixty-nine strictures were treated, with 65 (94%) strictures achieving resolution over 15 months. Increasing the number of stents has shown to improve success. In the group that successfully completed treatment, a total of 8 stents were used, with an average of 2.5 stents per ERCP. In the group with incomplete resolution of AnS, a total of 3.5 stents were placed.⁴⁸ Costamagna *et al.*⁴⁹ recommends balloon dilation followed by placement of maximum number of 10 Fr stents, and repeating ERCP every 3 months with stent stacking until complete resolution of the stricture on fluoroscopy. That study showed 80-95% success, with 20-35% recurrence.

In another series, the approach of placing a maximum number of stents with exchanges at 3 months had yielded a 90-94% success rate.^{48,49}

Temporary placement of a fully covered self-expanding metal stent (fcSEMS) has been looked at for AnS to try and reduce the number of ERCPs performed (Figs. 1 and 2). These stents are composed of stainless steel or nitinol.⁵⁰ The approach to placing fcSEMS begins with confirming the etiology, size and location of the stricture. If indeterminate, smaller than 5 mm or an intrahepatic stricture, one should avoid fcSEMS.¹⁰ Currently, 8 and 10 mm diameter fcSEMS are available in the USA and 8 mm stents should be used if duct size is 5-7 mm, and 10 mm self-expanding metal stent (SEMS) should be used if >8 mm.¹⁰ One drawback of fcSEMS is the higher risk of migration. The endoscopist can take precautions to prevent internal migration. Leaving the stent long in the duodenum, not dilating prior to stent placement, and centering the stricture on fluoroscopy before deployment are all strategies in managing migration of the stent. If a fcSEMS is successfully placed, there is a high success of stricture resolution. In one study of 200 patients, 80-95% of patients had stricture resolution after SEMS.⁵¹

Associated with SEMS placement was a 16% migration rate and reports of tissue ingrowth and stent impaction. In another study by Cote *et al.*¹⁰, 73 patients who underwent fcSEMS after liver transplant showed no difference in stricture resolution rate or number of days to resolution. Deviere *et al.*¹³ looked at 42 patients after OLT who had received fcSEMS for AnS and found resolution of strictures in 68% of the patients. More proximal strictures are even more difficult to access with fcSEMS. Overall, fcSEMS have not been shown to be superior to plastic stents.³⁰ Partially-covered SEMS provide a covered stent to manage the stricture, having theoretically lower migration rates, but removal can be problematic.⁵⁰ Some groups have placed a stent without sphincterotomy in a stricture after LDLT. For this, a piece of nylon is attached to the distal end of the stent to allow for removal.⁵² Overall, further data is needed before any type of SEMS becomes the standard of care for management of AnS strictures.

In approximately 4-17% of cases, ERCP cannot be performed due to inability to traverse the stricture with a guidewire.^{21-23,53,54} Single- or double-balloon enteroscopy, or spiral-assisted enteroscopy can allow for endoscopic access of an AnS after a Roux-en-Y construction. Wang *et al.*⁵⁵ demonstrated cannulation in 12 of 13 patients and successful intervention rate at 90% when using single-balloon enteroscopy. In a study by Shah *et al.*⁵⁶, a total of 129 patients that underwent enteroscopy then ERCP were studied. Ninety-two of the total patients (71%) had a successful enteroscopy (Single- or double-balloon enteroscopy, or over-tube enteroscopy). Of the 92 patients in which the AnS was reached, 88% had a successful ERCP intervention. Roux-en-Y AnS can respond to dilation and drainage via PTC. Percutaneous stents can be left in for a year. Liver enzymes are monitored closely and, if normal, the percutaneous stent can be removed.⁵

Some new ERCP balloons have been developed to improve AnS therapy outcome. Two small studies showed a peripheral cutting balloon is more effective than standard pressure balloons, with a long-term patency rate of 78% compared to 55%.^{57,58} Paclitaxel-eluting balloons have also been looked at for treating strictures. The hypothesis is that paclitaxel has antifibrotic properties which help to prevent fibroproliferation around the stricture.⁵⁹ Another technique that had been reported is intraductal magnetic compression.¹ In



Fig. 1. Anastomotic stricture 10 months after orthotopic liver transplantation.



Fig. 2. Placement of 10 mm × 6 cm partially covered self-expanding metal stent traversing the stricture.

this technique, magnets are placed on both sides of the AnS by PTC above and ERCP below. Approximation of the magnets then occurs to resolve the stricture. In one study, it was successful in 84% (10/12) of the patients studied. In follow up, restenosis occurred in 1 patient.⁶⁰ However, more studies are needed before cutting balloons, paclitaxel and magnet use become the standard of care.^{61,62}

Diagnosis of NAnS (hilar and intrahepatic)

NAnS result from hepatic artery thrombosis or ischemic damage to the duct, which are the main risk factors for this biliary complication. NAnS are found more than 5 mm proximal to the anastomosis.³⁰ NAnS can occur in both the extra- or intrahepatic ducts. The average time to NAnS development is usually 3–6 months.^{62,63} NAnS accounts for 10–25% of all strictures after OLT, with an overall incidence accounting for 1–15% of biliary complications.^{4,7,26,62–65} One theory suggests that the blood supply to the supraduodenal bile duct comes from vessels that are usually resected during OLT. In one study, 50% of patients with NAnS had no arterial collateral perfusion.⁶⁵ Op den Dries *et al.*⁵⁷ investigated 128 patients who had developed NAnS. Although those researchers found periductal vascular injury, the largest factor in NAnS may be the regenerative capability of the bile duct endothelium.^{38,58,61} Overall, the diagnostic algorithm usually follows the same pathway as AnS.⁶⁴

Management of NAnS

Dominant NAnS usually require a smaller balloon to dilate than AnS. Balloon size of 4 mm is typically used. Additionally, placement of only a single plastic stent (8.5–10 Fr) every 3 months is a common protocol.⁶² The efficacy of ERCP or PTC treatment is less than that of AnS, and these strictures

require a longer duration of treatment.⁷ There is a higher rate of stent failure due to migration or occlusion.¹

One study reported using 8.5–10 Fr, 12–20 cm fenestrated stent with multiple side holes in the treatment of a proximal NAnS.⁶⁶ The multiple side holes allow for circumferential drainage and represent a presumed advantage over Cotton-Leung or Amsterdam stents, which are rigid and have a single-end lumen. Jöhrin pancreatic wedge stents have been used in therapy of NAnS, due to their increased flexibility and side holes for drainage.⁵⁰ NAnS strictures that occur in the intrahepatic region of the biliary tree are difficult to access endoscopically. Studies have shown that an inability to cannulate a stricture in the hilum was the major reason for impaired stricture resolution with NAnS. If cannulation is achieved, 80–90% of strictures could be treated.^{39,63,67} If the patient is not a candidate for repeat transplantation, stricture radiotherapy has been shown to reduce rates of infection, obstruction, and graft failure.⁵

Digital cholangioscopy

Single-operator per-oral cholangioscopy (Spyglass DS System; Boston Scientific, Natick, MA, USA) has been used for evaluation of refractory or complex NAnS and AnS strictures. This instrument allows direct visualization inside the bile duct and for further evaluation of the stricture in question. Once visualization is achieved, a guidewire can be passed through the tight stricture and this facilitates therapeutic interventions.⁶⁸ Success rate with this method had been reported at 81% in one study.⁶⁹ Furthermore, direct visualization of the bile duct allows for further characterization of stricture either from erythema, edema, or ulceration to help guide endoscopic therapy and predict resolution of stricture.^{50,70} Strictures formed from edema respond better to therapy compared to ulcerated strictures.⁷⁰ Tissue sampling

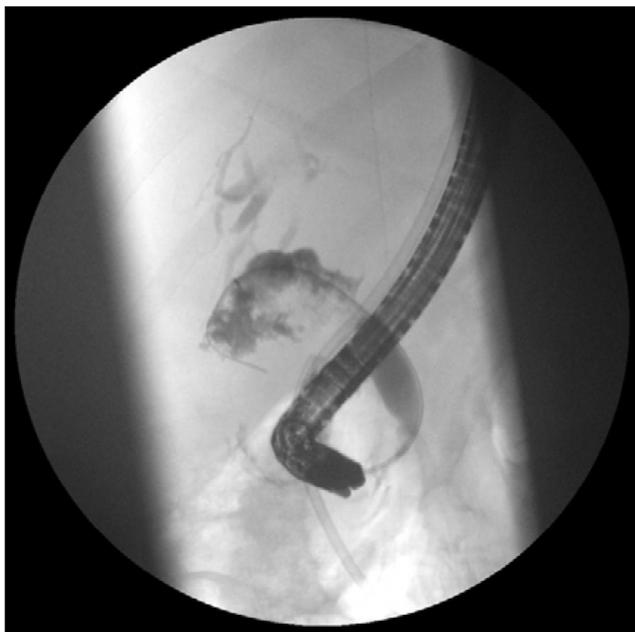


Fig. 3. Bile leak 4 months after orthotopic liver transplantation.

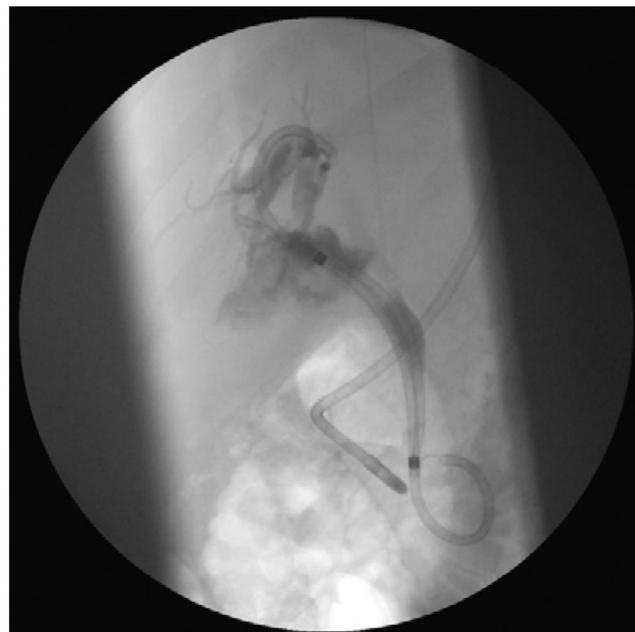


Fig. 4. Successful placement of two 10 Fr x 9 cm plastic stents traversing bile leak.

of strictures can be obtained if needed. A course of antibiotics should be given prophylactically, whenever direct cholangioscopy is used, due to the immunosuppression in the post-OLT patient causing an increased risk of bacterial translocation, as water irrigation is used for insufflation to visualize the duct.

Fifty percent of patients with NAnS have long-term response to PTC or ERCP therapy.^{3,5-7,28,62,63,71} If biliary tract therapy fails, Roux-en-Y choledochojejunostomy is usually performed with duct-to-duct anastomosis. If Roux-en-Y was already done, trimming the bile duct to the graft where there is evidence of good vascularization has been shown to prevent recurrence of the stricture.⁵ Replantation is also an option.

Bile leaks

Bile leaks occur in the range of 2–25% post-transplant.^{2-6,25,26,72,73} The majority of bile leaks will be seen 1 day to 6 months after transplant.^{1,74} ERCP is a very effective for both diagnosis and treatment of a bile leak, usually requiring on average two ERCP sessions (Figs. 3, 4, and 5).²⁷ A bile leak is a risk factor for strictures and vice versa. A bile leak can occur from the anastomosis, PTC tube tract, the cut surface of the liver (Luschka's duct), or from the cystic duct remnant.¹⁷ The anastomosis site is the most common.

In a review of 55 articles on bile leaks, 7.8% (668/8585) occurred amongst DDLT patients and 9.5% (268/2812) occurred with LDLT.⁷⁴ The diagnosis of bile leaks should be suspected in patients with fever and signs of peritonitis after liver transplantation or after T-tube removal. Some patients may not be symptomatic in the setting of immunosuppression. If there is elevation of bilirubin, change in cyclosporine levels or bile in ascitic fluid, one should raise the question of a bile leak.⁷⁵

US or CT/MRI can be pursued if there is a concern for a bile leak causing an extrahepatic collection. If there is a frank

collection seen, direct percutaneous drainage by interventional radiology should be considered. If no overt signs of a bile leak are seen on those imaging modalities, a hepatobiliary iminodiacetic acid (known as HIDA) scan has an 80% specificity and a 50% sensitivity for detecting a leak.^{76,77} Bile leaks are usually divided into two groups based on time of presentation (early or late).

Early bile leaks (<4 weeks)

Early anastomotic leaks usually occur because of technical problems related to surgery. Causes of bile leaks include active bleeding at the bile duct end, excessive dissection of periductal tissue at time of procurement, tension on ductal anastomosis, incorrect suture of the cystic duct stump, or use of electrocautery to control bleeding.⁵

Late bile leak (>4 weeks)

Late bile leaks are usually related to premature T-tube removals, at which time a fistula tract may have developed. Pain with removal of the tube may be suggestive of a bile leak, which can evolve into biliary peritonitis. In one study, 31% of patients with a T-tube reported a bile leak, with 7% being late.⁵

Management of bile leaks

If a T-tube is in place, bile flow will be diverted and will often times result in closure of the leak in 1/3 to 1/2 of leak closure within the first 24 hours.^{1,78} For the remaining patients, the majority will require ERCP with sphincterotomy and stenting or biliary diversion, with either through nasobiliary drainage. Treatment by ERCP with plastic stent has resolved early bile leaks in 90–95% of cases.^{5,6,79,80} Immediately



Fig. 5. Resolution of bile leak 2 months after placement.

post-operative, 25–33% of bile leaks will resolve spontaneously in 24 hours.⁷⁸ Usually, a sphincterotomy is performed, then a transpapillary stent is placed for 2–3 months to divert bile away from the leak.³⁰ This helps decrease the transpapillary pressure gradient that can exacerbate bile leaks.⁸¹ Longer duration of stent placement is recommended in OLT cases compared to the usual 4–6 weeks when a stent is placed post-cholecystectomy because of delayed healing in the setting of immunosuppression.³⁰ Bile duct clearance of stones and sludge should be performed after the stent is removed, as there is a high incidence of concurrent sludge or stones with bile leaks.⁸² fcSEMS have been looked at in treating bile leaks. In a small study with 17 patients, 47% (or 8) patients developed CBD strictures after removal of the stent.⁸³ fcSEMS after OLT can be considered in refractory leaks or larger bile leaks.⁸⁴ If a T-tube is in place after stenting, it should be removed in 1–2 days after successful stent placement.⁵

Roux-en-Y choledochojejunostomy bile leaks are rarer. The intestinal loop of the anastomosis may lead to the formation of intra-abdominal abscess and sepsis.⁵ Leaks after Roux-en-Y can be diagnosed by HIDA scan. ERCP is often difficult, given the anatomy. If unable to obtain biliary access endoscopically, a percutaneous internal-external drain can be used to drain bile leaks but surgery will be needed if these above measures fail. If successful, PTC with both an internal and external drain can be up-sized and used for 3–6 months until drainage has stopped.⁵ Another novel approach reported is a technique where a gastrostomy is formed using EUS and then ERCP is performed through gastrostomy port. Successful biliary intervention was achieved in 9/10 patients compared to the 58% success with deep enteroscopy.^{85,86} Nasobiliary tubes have also been effective in treating bile leaks. After the initial ERCP, a biliary drain is placed proximal to the leak.⁶⁸ These allow frequent cholan-

giograms in follow up (every 3–5 days) without repeat ERCP.⁸⁷ In one study, the average time to fistula closing was 6.3 days.⁸⁰ A drawback to this approach, however, may be diversion of bile from the intestine causing decreased drug reabsorption.

Bile duct stones

Filling defects can be seen after liver transplantation, due to stones, sludge, migrated stents, casts, or clots.⁵ Incidence of filling defects occurs between 2.5–12% post-OLT.^{3,6,25,64,88–90} Bile sludge can occur due to cyclosporine's increased lithogenicity. Strictures, ischemia, and infections predispose the formation of common bile duct (CBD) filling defects.^{5,27,72,91} Additionally, mucosal damage, ischemia, infection, foreign bodies, cholesterol supersaturation, and bile pool depletion may play a role in formation of stones.^{1,60,92} The median time for stone formation is 19 months and it is more common after OLT.

Management of bile duct stones

ERCP is the initial therapeutic test to remove bile duct stones. Overall, ERCP is successful in 90–100% of patients for clearance of stones.^{17,24} There was a 17% recurrence rate of an obstructing stone within 6 months of removal of the initial stone, in one study.³ In another study, two sessions were required in 24% of patients, and three or more sessions were required in 17% of patients.^{93,94} Ursodiol can be considered as a preventive against formation of stones, but more research needs to be done to define its long-term efficacy.⁵

Biliary cast syndrome

Biliary cast syndrome marks the presence of multiple, hard, and pigmented brown casts causing obstruction. Reported incidence is 2.5–18%.^{18,95} Biliary cast syndrome was present in 2.5% of patients in one retrospective OLT study looking at 355 transplantations.^{90,96} The etiology of biliary cast syndrome is thought to be from acute cellular rejection, ischemia, infection, and biliary obstruction from stasis.¹ Damage of the biliary tree mucosa can cause formation of desquamated epithelial cells (casts) combined with lithogenic bile.⁹⁷ Increased risks for this syndrome include hepatic artery stenosis and strictures.⁹⁶ In one study, ERCP was successful in treating 60% of patients with biliary cast syndrome.⁹⁸ If casts develop in a patient with a Roux-en-Y, percutaneous access should be attempted to remove casts.

Biloma

Most bilomas will occur outside the liver in the perihepatic space. The incidence is not well defined, but one study by Said *et al.*⁹⁹ reported an incidence of 11.5%. Small bilomas are oftentimes self-limiting.⁹³ Larger bilomas should be drained percutaneously and antibiotics should be given. If it occurs within the liver amongst the biliary tree, transpapillary stent and endoscopy can be used for management; however, ERCP is often diagnostic and not therapeutic. If no communication is present, percutaneous drainage and antibiotics should be used. Taking a transgastric approach via endoscopic US is another option to drain bilomas.⁵⁰ Surgery is indicated when the biloma cannot be controlled with the above management.

Hemobilia

Hemobilia can occur after PTC or biopsy.¹⁰⁰ It is an uncommon presentation, reported in one study to have a frequency of 1.2% in 2701 patients.⁷⁶ In another study of 33 patients with hemobilia, ERCP placement of nasobiliary drainage improved symptoms in 87.9%.⁷⁶ For significant hemobilia, careful angiographic therapy should be used to achieve hemostasis. If there are evidence of clot formation, ERCP can be used for clearance of the bile duct.

Mucocele

A mucocele is a collection of mucous from cells lining the cystic duct remnant, causing compression of the bile duct.^{77,101,102} It is a rare biliary complication in the post-transplant patient. On US, mucocele will appear as a fluid collection in the porta hepatis. Yet, diagnosis is usually not made for weeks to years.⁵ It should be distinguished from other radiographic findings that appear similar, including abscess, biloma, hemobilia, tumor, or aneurysm. Diagnosis can be confirmed with MRCP.⁵ Surgery or drainage from the cystic duct bed is usually the management course. Endoscopic therapy has not been shown to be effective and is not recommended.¹⁰²

Redundant CBD

A rare biliary complication that has been described in the literature is a redundant CBD after OLT. The donor duct can be longer than the recipient's CBD, causing a sigmoid-shaped loop that can cause cholestasis, leading to biliary complications.¹⁰³ Incidence has been reported to be 1.6% of all OLT. In

80% of patients, the loop resolved after placing a long plastic stent. If that fails, Roux-en-Y hepaticojejunostomy is the next definitive step.¹⁰³

Bactobilia

The clinical significance of bactobilia is not known, but may be a risk factor in development of biliary complications. In one study, bile samples were collected from 66 patients post-OLT, with 73% of the patients being positive for microorganisms. Forty-eight percent had Gram-positive bacteria, 39% had Gram-negative, 3% had anaerobic bacteria and 9% had fungi.¹⁰⁴ Nineteen patients out of the 66 with bactobilia experienced clinical signs of cholangitis.¹⁰⁴ All 19 of these patients were papillotomized and all but one had insertion of a plastic stent for therapy.¹⁰⁴ More studies need to be performed looking at the clinical impact of bactobilia.

Biliary complications following LDLT

Due to lack of availability of cadaveric livers, LDLT has gained increasing popularity with adult patients in recent years.³⁰ Biliary complications are frequent after undergoing LDLT and the anatomy is often difficult, as Roux-en-Y hepaticojejunostomy and Roux-en-Y gastric bypass are encountered after transplant.⁵⁰ Ductal devascularization of the right hepatic duct stump at time of harvesting often causes more prolonged ischemia time, increasing biliary complications.⁸¹ During LDLT, the recipient's common hepatic duct needs to be divided in the hilum to avoid tension at the anastomosis. This oftentimes alters the blood supply to the hepatic duct stump, which comes from the gastroduodenal artery below.¹⁰⁵⁻¹⁰⁷

Overall incidence of complications is 6–40%, with leaks occurring in 22% of patients, and 40% developing strictures.¹⁰⁸ There is 2–3-times increased risk of biliary complications with LDLT. Risk factors are similar to those of DDLT and include age and gender, ABO compatibility, cytomegalovirus infection, biliary leakage, multiple ducts for anastomosis, and type of reconstruction performed.¹⁰⁹⁻¹¹¹ ERCP is more difficult in LDLT recipients. The ducts are smaller with LDLT, require the use of smaller balloons, and the placement of small 7 Fr stents in the strictures, requiring multiple ERCPs with stent exchange.³⁹

Stricture resolution is lower in LDLT than in DDLT, with a range of 31% to 85%. The most common reason for failure is inability to access the small bile duct branches.^{7,25,53,112} Median time to onset of a biliary stricture is 5.9 months in one study looking at LDLT patients.⁶⁴ Hsieh *et al.*⁵¹ looked at 110 patients retrospectively who had undergone LDLT and duct-to-duct anastomosis. This study was looking at the outcomes of endoscopic approach to AnS after LDLT with dilation and multiple stent placement. Thirty-two out of thirty-eight (84%) had successful resolution of strictures after endoscopic treatment. No patients needed retransplantation or surgical intervention.⁵¹ Tsujino *et al.* looked at 174 patients that underwent LDLT with duct-to-duct biliary reconstructions. Complications developed in 53 (30%) of the patients. Seventeen patients had endoscopic intervention for a biliary stricture. Twelve patients (71%) had successful treatment of the stricture. Bile leaks occur at higher frequency in LDLT due to the cut edge of the transplanted liver. Because of higher risk of failure with LDLT, PTC or surgery are backup modalities for treatment of refractory biliary complications.

Donors may also experience complications in LDLT. In 200 donors looked at, 26 had bile leaks (13%) and 3 had strictures

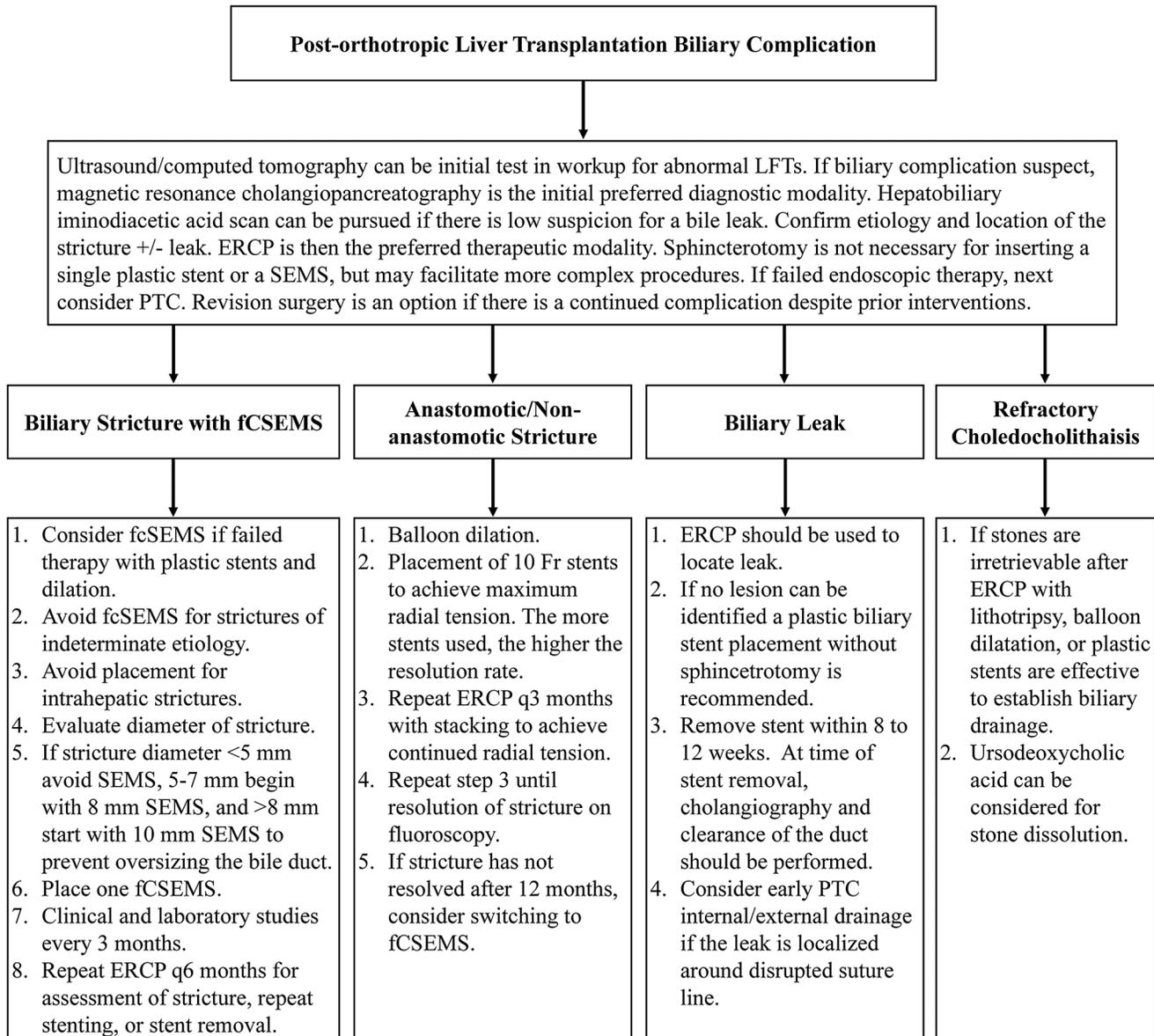


Fig. 6. Decision tree for managing biliary complications after orthotopic liver transplantation.^{1,82} Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; fcSEMS, fully covered self-expanding metal stent; PTC, percutaneous transhepatic cholangiography; SEMS, self-expanding metal stent.

(1.5%) in the monitoring period of 28.7 months.¹¹³ In a study of 1508 donors in Asia, more complications were associated with right-lobe than left-lobe or left lateral transplantation.¹¹⁴

Conclusions

Biliary tract complications are often seen complicating OLT, with an overall incidence of 10–25%. The possibility of a biliary complication should be raised in the presence of a fever, right upper quadrant abdominal pain, or increased white blood cell count and LFTs. Initial evaluation should begin with Doppler US and consideration of advanced imaging with MRCP. MRCP is a good test to establish the initial diagnosis and assess the biliary system if there is a low likelihood of a biliary complication.¹¹⁵ If significant biliary

pathology is suspected, ERCP and or PTC should be utilized primarily for therapy.

Strictures are best treated with balloon dilation with routine stent exchanges. Most patients will require 3–5 ERCPs, with multiple plastic or metal stents placed and exchanged for at least a year before stricture resolution (Fig. 6).¹¹⁵ If there is a bile leak, ERCP stent exchanges should occur at 2–3 month intervals, due to concern over immunosuppression.¹¹⁵ Although rarer, common duct stones, biliary cast syndrome, mucocele, bilomas, and hemobilia can be managed with ERCP or PTC. ERCP and/or percutaneous intervention can avoid repeat surgery. Early identification and aggressive treatment of these complications have shown to improve morbidity, mortality, and graft survival after liver transplantation.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Wrote the manuscript and reviewed the literature (BTM), revised and edited the manuscript for important intellectual content and format (JWB).

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