Biliary Complications after Liver Transplant: Timeline, Spectrum, Management Algorithm, and Prevention

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Abstract

Biliary complications are the most common complications seen after liver transplantation (LT) with an incidence ranging between 10 and 15% and increasing in the setting of increased access to living donor liver transplant and utilization of marginal grafts. Among the biliary complications, the most common are anastomotic strictures, nonanastomotic strictures, and biliary leaks, which have a variable time of presentation posttransplant. The risk factors for the development of biliary complications include surgical techniques, type of grafts, prolonged ischemia, primary disease etiology, and associated post-LT complications. The approach to a diagnosis in an appropriate clinical setting involves a stepwise approach involving clinical history, assessment of risk factors, biochemical abnormalities, and appropriate imaging. Therapeutic options revolve around endoscopic retrograde cholangiopancreatography and percutaneous transhepatic biliary drainage, with surgical intervention being reserved in case of failure of these modalities. Preventive strategies with machine perfusion techniques are promising, while use of T-tubes for prevention of complications remains controversial.

Keywords
- anastomotic stricture
- nonanastomotic stricture
- biliary leak

Introduction

Liver transplantation (LT) has globally emerged as the most successful treatment option for patients with end-stage liver disease and hepatocellular carcinoma with excellent 5-year survival rates.[1] With widespread access and expanding numbers of LT, it is imperative that post-LT complications are also increasingly being encountered. The three common complications post-LT are vascular, infective, and biliary, with the last being the most common.[2] The incidence of biliary complications (BCs) is variable, ranging from 10 to 15% in deceased donor liver transplant (DDLT) settings and reaching up to 15 to 30% in living donor liver transplant (LDLT) settings, and this increases further with the use of liver grafts from non-heart-beating deceased donors.[3,4] The most common types of BCs include anastomotic strictures (AS), nonanastomotic strictures (NAS), and biliary leaks. Other uncommon complications include bile obstruction due to stones, sludge, biliary casts, sphincter of Oddi dysfunction (SOD), and hemobilia (►**Table 1**). Recognizing all these complications is paramount to preventing graft loss, morbidity, and mortality. Therapeutic options include endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic biliary drainage (PTBD), with surgical intervention being reserved in case of failure of these modalities. In this review, we summarize the evidence regarding post-LT BCs with reference to the spectrum, timeline, and management algorithm.

Risk Factors

In a systematic review involving 14,411 transplanted patients with BCs, the significant risk factors identified were preoperative hyponatremia, advanced liver disease, presence of primary sclerosing cholangitis or malignancy, donor factors (age >60 years, graft steatosis), surgical factors

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Table 1 Types of post-LT biliary complications with usual timelines and incidence

Type of complication	Presenting features	Timing	Incidence (%)
Anastomotic strictures	Asymptomatic biochemical cholestasis Jaundice Cholangitis	Early or late Mostly within the 1st year but can be as late as 10 y	6–12
Nonanastomotic strictures	Asymptomatic biochemical cholestasis Jaundice Cholangitis	Early in the 1st year usually ischemic Late usually has multifactorial etiology	10–16
Biliary leak	Elevated liver enzymes Fever Bilious output in drains Peritonitis	Early (within 3 mo): local ischemia or surgical complication Late: removal of the T-tube	8–12
Bile duct filling defects	Biochemical cholestasis Jaundice	Late	3–8
Sphincter of Oddi dysfunction	Abdominal pain Biochemical cholestasis	Variable	2–3

Abbreviation: LT, liver transplantation.

(duct-to-duct anastomosis, long anhepatic phase, prolonged cold ischemia time, use of T-tube), and post-LT complications (acute cellular rejection, cytomegalovirus [CMV] infection, hepatic artery thrombosis [HAT]; ►**Fig. 1**).[5]

The Spectrum of BCs after LT

Anastomotic Strictures and Nonanastomotic Strictures

By definition, AS are isolated strictures located within 1 cm of the biliary duct anastomosis of the donor and recipient and have an incidence of 6 to 12%.[2,6] AS can develop as early as a week to up to 10 years post-LT but is usually seen within the first 1 year after LT.[4] AS have been classified as early or late with early AS occurring within 3 months of LT.[1] Pathophysiologically, the development of early AS is usually attributed to surgical techniques (size mismatch, narrowing due to edema, bile leak, tension at anastomosis site), while late-onset AS tend to arise due to local ischemia, which leads to a fibrotic process around the anastomosis.[7,8] The risk factors associated with the development of AS include the type of graft used during LT (LDLT and split liver grafts being

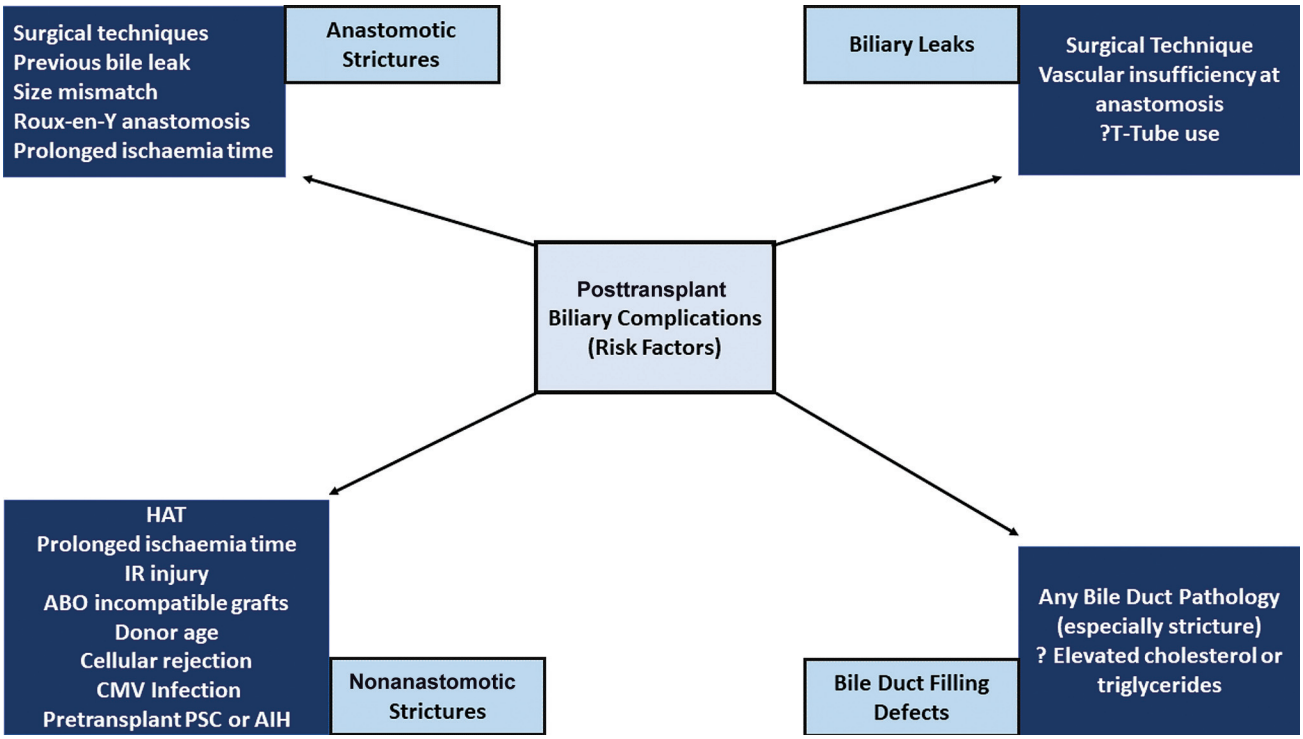

Fig. 1 Risk factors for post–liver transplant biliary complications. AIH, autoimmune hepatitis; CMV, cytomegalovirus; HAT, hepatic artery thrombosis; IR, ischemia reperfusion; PSC, primary sclerosing cholangitis.

most susceptible), postoperative bile leaks, male/female mismatch, prolonged ischemia times, and complex surgical reconstructions[2,9]

NAS are strictures, irregularities, or dilatations located beyond 1 cm from the anastomosis. These are usually difficult to treat and are frequently associated with the development of casts and sludge in the biliary tree. The median time for presentation of NAS is 6 months although they can frequently present later with an estimated incidence of 10% at 1 year to 16% post-LT at 10 years.[7,8] These can be seen in both the extrahepatic and intrahepatic bile ducts and are usually associated with HAT, while those occurring without HAT are often referred to as ischemia type biliary lesions (ITBL). Besides HAT, other risk factors associated with NAS are longer ischemia time, ischemia reperfusion injury, donation after cardiac death (DCD grafts), ABO-incompatible (ABOi) grafts, prolonged and complicated postoperative course, primary sclerosing cholangitis as a primary disease etiology, graft rejection, and CMV infection.[8] Importantly, the use of DCD grafts has been associated with a 10-fold higher risk of development of NAS with older age of graft, hyperbilirubinemia immediately after transplant, and higher international normalized ratio (INR) in the first 7 days being possible indicators.[10,11] While HAT has been a classical association for NAS, the occurrence of NAS in the absence of HAT has given rise to multiple postulates in pathogenesis. An emerging theme is the failure of regeneration of the bile duct because of injury to the peribiliary vascular plexus and peribiliary glands, which are thought to have a regenerative capacity.[12] While outcomes of ABOi LT has progressively improved, biliary strictures (BS) still remain a major concern. One study reports 1- and 3-year BS-free survival rates of 81.5 and 79.0%, respectively, which were significantly lower than compatible transplants.[13] A graft bile duct opening diameter less than 5 mm, antecedent acute cellular rejection, and ABOi itself were independent risk factors. Diffuse intrahepatic BS exclusively occurred in 12 patients (8.5%).[13]

Biliary Leakage

Similar to BS, biliary leaks can be anastomotic or non-anastomotic. The incidence of bile duct leakage post-LT ranges between 8 and 12% originating from either the bile duct or, rarely, the cystic duct and can be associated with biloma formation. Data from a meta-analysis of 11,937 patients showed an incidence of 7.8 and 9.5% in DDLT and LDLT settings, respectively, presenting usually between 1 and 6 months after LT.[4] Literature from India from 338 LDLTs showed an overall BC rate of 19%, of which 54% had BS, while 46% had biliary leak.[14] The risk factors of the development of biliary leaks are similar to those of AS and are predominantly a function of surgical techniques and complications. The incidence of bile leak has been shown to be higher with Roux-en-Y (RY) anastomosis compared with duct-to-duct anastomosis, although a recent systematic review focusing on primary sclerosing cholangitis has shown similar event rates.[15,16] Biliary leaks from the cut surface of the liver originating from small bile ducts transected during hepatic resection are seen in the LDLT setting, but are less likely to endanger the graft.[3] Additionally, in cases of HAT or prolonged ischemia, biliary leak can be massive and occur from multiple sites.[2] The practice of T-tube placement after biliary anastomosis remains controversial both with regard to biliary leaks and subsequent BS formation.[17]

Posttransplant Bile Duct Filling Defects

Post-LT bile duct filling defects include a variety of abnormalities, including biliary stones, sludge, and casts reported in 3 to 6% of the patients.[8,18] The essential pathophysiology lies in the development of biliary stasis due to any reason, which may include BS, ischemia, infection, cellular rejection, and medications.[8] BS in this context is an important risk factor with up to 45% of patients with bile duct filling defects having a simultaneous stricture.[1] In a case-control study involving 49 cases with bile duct stones matched with 101 controls, the presence of any bile duct pathology, total cholesterol $\geq$ 200 mg/dL, and triglyceride levels $\geq$ 150 mg/dL were shown to be risk factors for post-LT bile duct stone formation, while the use of ursodeoxycholic acid was found to be protective.[18] Biliary casts refer to the development of hard casts in the biliary tree, usually composed of bilirubin and bile acids. In a recent study spanning 311 LT, 14 (4.5%) cases of biliary casts were identified, with a classic "duct-in-a-duct" appearance on T1-weighted magnetic resonance imaging being a common finding.[19] Importantly, the study showed 40% of patients developing recurrent strictures and having lower overall and graft survival compared with patients with AS or NAS without associated biliary casts.[19]

Miscellaneous BCs

Other BCs included SOD and vanishing bile duct syndrome (VBDS). Biliary sphincter dysfunction after LT has been poorly described. In a recent review involving 1,307 post-LT patients, 13 patients (1.0%) satisfied the updated Rome IV criteria for papillary stenosis (previously SOD type I) and 14 patients (1.0%) met the Rome IV criteria for functional biliary sphincter disorder (FBSD; previously SOD type II). Importantly, all cases suspected to have FBSD eventually had a different diagnosis on follow-up, thus questioning the presence of an FBSD after LT.[20] VBDS is a rare complication resulting from loss of small bile ducts and is usually associated with acute or chronic cellular rejection. Other associations like CMV infection and medications have been postulated, but this lacks conclusive evidence. Resolution is extremely unpredictable and frequently requires re-transplantation.[8]

Biliary Complications in LDLT Settings

LDLT as compared with DDLT has been associated with a higher incidence of BCs and more challenging strictures for endoscopists/intervention radiologists. In the setting of a smaller graft as compared with DDLT, the donor duct caliber is smaller, leading to disparity between the recipient and donor ducts.[21] The smaller overall graft size in LDLT leads to

smaller duct size and higher anastomosis. Certain observations suggest that a short right hepatic duct with a long caudal right posterior duct is associated with a significant risk of BCs because of the thinner biliary wall of the posterior duct. Therefore, an LDLT donor with a single graft duct potentially is the best means of reducing BCs in the recipient.[22,23] Similarly, bile duct division in the donor should be preferably done under real-time fluorescence imaging even in laparoscopic procedures, in order to not compromise safety for the donor and to reduce BCs in the recipient. BCs tend to persist longer and require multiple interventions.[24] Multiple anastomoses as well as angulations between the extrahepatic bile duct and the new liver are associated with ischemic risks and adjacent tissue traction.[23] Even with aggressive stenting and use of fully covered self-expanding metal stents (FCSEMS), re-stricturing has been reported.[23]

Approach to Diagnosis of BCs after LT

The clinical manifestations of BCs after LT have certain common themes ranging from asymptomatic abnormalities in liver function tests and clinical cholestasis to cholangitis and biliary peritonitis. The cardinal differential diagnosis always includes HAT, cellular rejection, sepsis, and infective hepatitis post-LT.[2] A key step in proceeding with BCs after LT is to assess the pretest probability. Various factors including risk factors as mentioned before, type of surgery, ischemia time, and the clinical setting of presentation provide important clues to the type of BCs. The first diagnostic modality is an ultrasound (US) to assess the diameter of the bile ducts along with a Doppler to assess hepatic artery patency. If Doppler is inconclusive for adequate HA flow, then the next step is a computed tomography angiogram (CTA). Besides confirmation of HA status, CTA is often useful to rule out other complications (collections, abscess). Once the CTA confirms patent HA, the next step is evaluation of biliary tree with magnetic resonance cholangiopancreatography (MRCP). MRCP has been shown to have a similar diagnostic accuracy for BCs after LT as direct cholangiograpic modalities like percutaneous transhepatic cholangiography (PTC) or ERCP.[25,26] The next step involves ERCP and/or PTC with a therapeutic intent (PTBD) depending on the anatomy and type of anastomosis. A diagrammatic approach to BCs after LT is shown in ►**Fig. 2**.

Management of BCs Post-LT

While in the past surgical revision was frequently required for post-LT BCs, the current standard of care is ERCP- and PTC-guided interventions like PTBD. The choice between ERCP and PTC depends on the primary type of anastomosis (duct-to-duct anastomosis vs. hepaticojejunostomy), anatomy and location of primary defects, and overall clinical status of recipients, with endoscopic treatment being the preferred first choice whenever feasible. The timing of intervention lacks consensus with most centers avoiding ERCP in the first few weeks after LT. Strictures developing early (within 6 months) usually respond better to ERCP, and delay in treatment has been shown to be associated with poor outcomes.[21] Surgical revision is reserved for strictures refractory to either ERCP or percutaneous

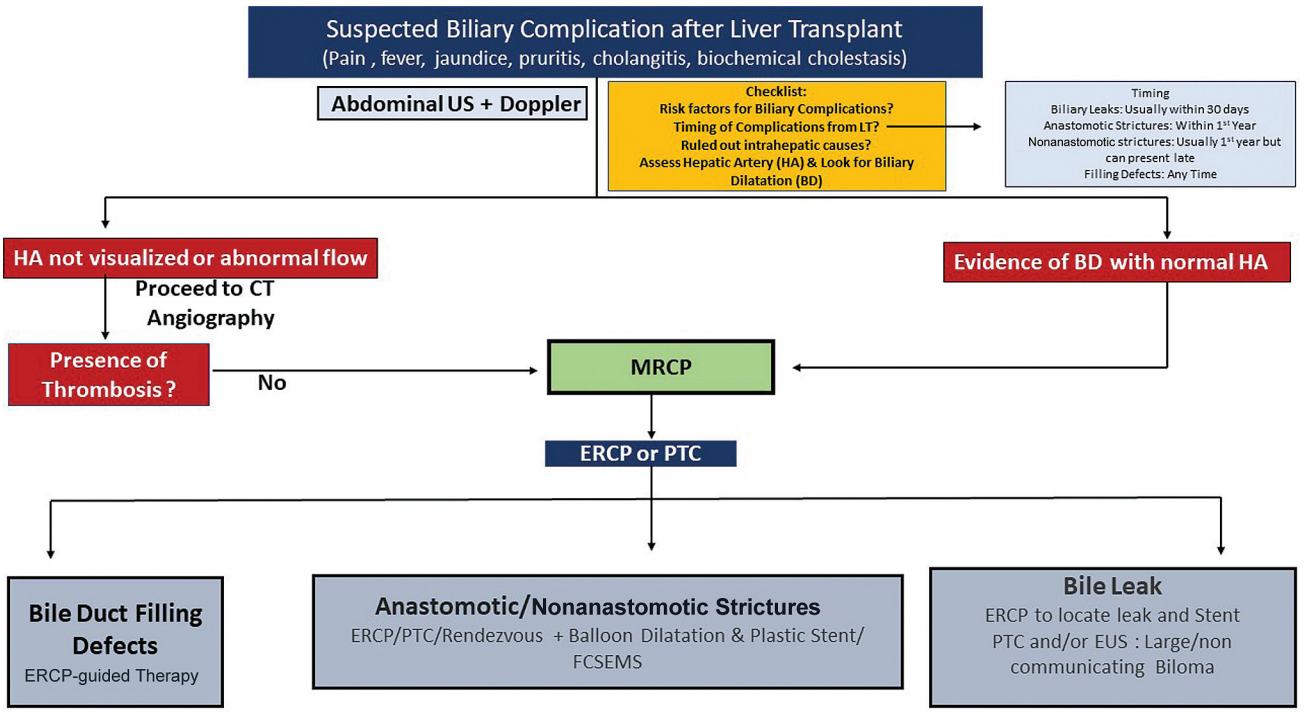

Fig. 2 An algorithmic approach for diagnosis and treatment of common biliary complications after liver transplantation. ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FCSEMS, fully covered self-expanding metal stents; MRCP, magnetic resonance cholangiopancreatography; PTC, percutaneous transhepatic cholangiography; US, ultrasound.

therapy and in whom retransplant is the last resort after all other treatment modalities have failed. When surgical revision is required for patients with a duct-to-duct anastomosis, the procedure most commonly performed is an RY hepaticojejunostomy.[27] If a hepaticojejunostomy was the initial modality, then an attempt is made to reposition the bile duct graft to a better vascularized area.[27] Brief reports of robotic hepaticojejunostomy have been described showing them to be safe, requiring shorter duration of stay compared with open reconstruction as well as effective not requiring revision surgeries.[27] Additional liver resection has been described in settings of BCs, and abscesses in small series have been shown to have acceptable complication and survival rates as compared with retransplantation.[27,28]

Management of AS

Endoscopic therapy of AS involves balloon dilation of the stricture with or without placement of stents (plastic or metal). Balloon dilation alone, although a successful initial modality, is associated with a high rate of recurrence; hence, the current standard of care is placement of a biliary stent.[29] Following balloon dilation of 4 to 10 mm, depending on donor duct size and time elapsed since LT, 7- to 10-Fr plastic stent is placed with (►**Fig. 3**) revision of procedure in 2 to 3 months, wherein the stricture is again dilated, and one or more plastic stents are replaced.[30] Usually, two to four stents are placed in repeated sessions in a "progressive stenting" approach, whereas some authors propose a "maximal stenting approach" wherein six to eight stents are placed at a given session.[31] Another technique that has been utilized is the addition of stents without the removal of prior stents, which has also been shown to have similar outcomes.[32] Given the repeated number of procedures required with plastic stents, FCSEMS have been used as an alternative modality as they have a larger diameter and are less prone to stent occlusion. In a recent meta-analysis of four randomized controlled trials, resolution rates of AS, adverse events, and stent migration rates were similar between FCSEMS and plastic stents, with the FCSEMS strategy requiring less numbers of ERCPs.[33] A recent long-term follow-up study involving 33 patients who had FCSEMS removal between 4 and 6 months showed a 5-year probability of remaining stent free of 60.9%, showing it to be a viable option post-LT.[34] However, it is important to note that endoscopic success rates in DDLT and LDLT setting are different and not comparable due to the presence of multiple ductal anastomoses and the small caliber of the ducts in LDLT recipients, making an ERCP a more technically difficult procedure.[2] Historically, the PTC approach has been the treatment of choice in cases with bilioenteric anastomosis (RY construction). However, balloon enteroscopy (single or double) or spiral-assisted enteroscopy has been shown to be useful to allow access in such cases.[35,36] Recently, biodegradable stents placed by percutaneous routes have been shown to be useful in difficult-to-treat AS with a complete resolution rate of up to 72% after a median follow-up of 27.2 months.[37] Another novel concept is based upon the principle of intraductal magnetic compression wherein magnets are placed by ERCP and PTBD, and stricture resolution is attempted by magnet approximation.[38]

Management of NAS

In contrast to AS, NAS are more complex. Strategies vary depending on the anatomy, and results are inferior. Approaches are similar to AS, with serial balloon dilation and progressive stenting being used, but usually involve smaller balloons and fewer stents. However, they are frequently complicated by sludge and casts mandating more frequent stent exchange. [39] For intrahepatic NAS not accessible to ERCP, a PTC-based technique or a combination (rendezvous technique) of PTC and ERCP is used. Unfortunately, NAS strictures tend to progress despite

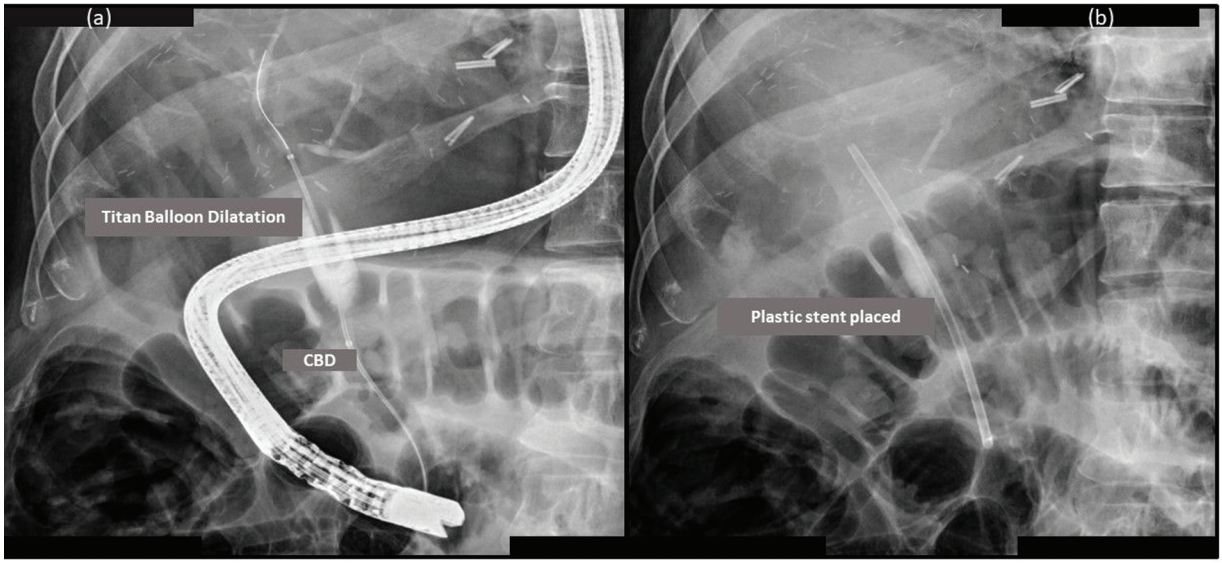

Fig. 3 Demonstration of post–liver transplant stricture intervention. (**a**) Balloon dilatation of stricture. (**b**) Biliary stent placement.

seemingly adequate management in more than half the cases and rates of re-transplantation vary between 16 and 50%.[40,41]

Management of Bile Leaks and Biloma

In rare cases of asymptomatic small biliary leaks, conservative management may suffice. If a T-tube is in place, bile flow gets diverted, resulting in the closure of the leak, although the routine placement of a T-Tube is by itself a controversial issue. However, in most cases with significant biliary leak, ERCP with sphincterotomy and biliary stenting is required and has a success rate between 88 and 95%.[42] The principle of stenting is to act as a "bridge" and decrease the transpapillary pressure gradient, which exacerbates leaks. ERCP should be repeated in 4 to 6 weeks to assess leak resolution and need for stent upsizing, although some advocate a comparatively longer duration of stent placement because of delayed healing in an immunosuppressed setting.[30,43] Percutaneous approaches using internal–external drain with stents is the usual approach with a fair success rate although inferior to non-LT biliary leaks.[44,45] In the cases with biliary leak with duct disruption or bile duct necrosis and with patients with severe abdominal sepsis with hemodynamic instability, surgical interventions are frequently required. Bilomas are often self-limiting, but larger bilomas require intervention. If the biloma is confined within the liver along the biliary tree, ERCP and stenting should suffice. However, if no communication is present, the percutaneous approach is the preferred route. Endoscopic US using intragastric approaches can serve as an alternative modality.[36] In some situations of refractory biliary leaks and complex leaks, embolization can be performed using liquid embolics, coils, or alcohol as a sclerosant.[46]

Preventive Strategies

Use of T-Tube/Stents in the Prevention of BCs

The use of a biliary drain in the form of a T-tube with one end inside the bile duct anastomosis and the long limb of T-tube draining outside has been historically advocated for the prevention of BCs. A previous meta-analysis ($n = 639$) of 15 retrospective studies and 5 were randomized controlled trials showed a higher incidence of strictures in those having reconstruction without a T-tube (14 vs. 31 events; odds ratio [OR] = 0.46; 95% confidence interval [CI] = 0.23–0.9).[17] More recently, an updated meta-analysis ($n = 3{,}320$) showed a higher incidence of overall BCs (OR: 1.54; 95% CI: 1.06–2.24) and bile leaks in the T-tube group, but higher odds of BS in those without T-tube.(OR: 0.60; 95% CI: 0.47–0.78), thus hinting at its possible use in patients with high risk of strictures.[47] In this context, an expert panel consensus suggested against the routine use of T-tubes due to the potential risk of biliary leakage and infections, with consideration for T-tubes in cases of high risk for BS.[48] Intraductal stents have also been studied, with a study from Jung et al suggesting lower overall rate of BCs in the stent group.[49] However, other studies and results from a recent meta-analysis have indicated contrary viewpoints.[50,51] Biodegradable stents have also been shown to be safe in the setting of liver transplant.[52] Results from small studies have shown excellent patency with duct-to-duct biliary reconstruction using an absorbable internal stent.[53]

Machine Perfusion in the Prevention of BC

As discussed previously, some of the key risk factors for the development of NAS include prolonged ischemia time and use of extended criteria grafts, especially with DCD grafts. Machine perfusion (MP) techniques (normothermic, subnormothermic, hypothermic) have been promising in the prevention of the development of post-LT BS.[54] Over the last 5 years, multiple studies have looked into hypothermic MP in the prevention of both AS and NAS.[55] In a recent landmark randomized trial with 156 patients who underwent DCD, the occurrence of NAS was significantly lower in the hypothermic oxygenated MP group (6 vs. 18%; risk ratio: 0.36; 95% CI: 0.14–0.94; $p = 0.03$) with the cumulative number of treatments for NAS being four times lower.[56]

Magnetic Compression Anastomosis in Treatment of BCs

In some patients with BBS after LDLT, AS may be completely occlusive wherein guidewires cannot be passed. In such cases, magnetic compression anastomosis has emerged as an alternative modality to reduce morbidity and mortality, and prevent reoperations.[57] The overall clinical success rate of magnetic compression anastomosis has been reported to be 87.5%, with a recurrence rate of 7.1%.[38]

Antibiotic Use

The pooled incidence of infections in post-LT undergoing ERCP is reported around 1.1% and studies have reported that prophylactic antibiotics may not lower the risk of infections or adverse outcome.[58] Based upon evidence, recent society recommendations provide for an individualized approach for administering antibiotics based on each patient's unique biliary anatomy and clinical condition, and advocates antibiotic administration in whom complete biliary drainage is technically challenging to achieve (ischemic cholangiopathy, multiple strictures, failure of stenting), to reduce infectious complications.[58]

Conclusion

BCs are the most common complications following LT. The incidence, timing, and nature of complications vary with type of transplant, surgical techniques, graft quality, and associated complications. Presentations can range from asymptomatic liver function abnormalities to life-threatening sepsis. Appropriate imaging and early intervention by endoscopic and/or percutaneous approaches, depending upon the anatomical characteristics, form the mainstay of therapy. MP techniques show promise as preventive strategies for grafts at high risk of complications.

Authors' Contributions
A.R. was responsible for conceptualization, writing of the original draft, and visualization. M.K.G. was responsible for writing (review and editing), supervision, and resources.

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Conflict of Interest
None declared.

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