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EDITORIAL

Role of endoscopy in the conservative management of biliary complications after deceased donor liver transplantation

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Abstract

The clinical outcome of patients receiving liver transplantation could be significantly affected by biliary complications, including strictures, leaks, stones and bilomas; early diagnosis and treatment of these conditions lead to markedly reduction in morbidity and mortality. Therapeutic gold standard is represented by conservative approaches, both endoscopic and percutaneous, based on the type of biliary reconstruction, the local availability of the procedures and specific expertise. In patients with previous transplantation, the difficult biliary access and the possible presence of concomitant complications (mainly strictures) further restrict the efficacy of the endoscopic and percutaneous treatments; on the other hand, surgery should generally be avoided because of the even increased morbidity and mortality due to technical and clinical issues. Here we review the most common biliary complications occurring after liver transplantation and discuss available treatment options including future perspectives such as endoscopic ultrasound-guided biliary access in patients with Roux-en-Y choledocho-jejunostomy or extracorporeal shock wave lithotripsy for difficult stones.

Key words: Endoscopic ultrasonography; Endoscopic ultrasound; Percutaneous trans-hepatic drainage; Endoscopic retrograde cholangiopancreatography; Biliary drainage

Core tip: The clinical outcome of patients receiving liver transplantation could be significantly affected by biliary complications, including strictures, leaks, stones and bilomas; early diagnosis and treatment of these conditions allow to markedly reduction in morbidity and mortality. With the continuous increase of endo-

scopic knowledge and expertise, the interventional management of these conditions is constantly evolving toward a conservative approach. In this manuscript are summarized current evidences regarding conservative approaches to biliary complication, with an overview on future management and research areas.

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INTRODUCTION

Orthotopic liver transplantation (LT) has become the standard treatment for end-stage liver disease and hepatocellular carcinoma[1]. Despite continuous surgical improvement, biliary complications are still considered one of the most common issue after transplantation: 10%-40% of cases report duct stricture (anastomotic and non-anastomotic), leaks, stones-sludge or cast, sphincter of oddi dysfunction (SOD), biloma, hemobilia, ductopenia (due to chronic ischemia or rejection), cholestatic recurrency of the underlying liver disease and, finally, biliary cast syndrome[2].

The type of biliary reconstruction, ischemia and reperfusion injury, hepatic artery thrombosis, cytomegalovirus infection and primary sclerosing cholangitis are the principal risk factors for the development of post-LT biliary morbidity[3,4].

In this difficult setting, conservative approaches are usually preferred: Endoscopic treatments include sphincterotomy, plastic or metallic stenting or multi-stenting, balloon dilation, stone clearance using various devices (*i.e.,* balloon catheter, Dormia basket), placement of naso-biliary tube; placement of external or internal-external drainage, stenting and balloon dilation are the most common percutaneous treatment options. Finally, surgery is usually avoided and confined after failure of conventional approaches[5,6].

The occurrence of biliary complications after LT could lead to recurrent hospitalizations and, even, to graft failure; the early detection and management of those conditions could reduce the increased costs with a significant improvement in post-transplant quality of life and survival[7,8].

The clinical presentation could be ambiguous, ranging from severe acute manifestations (cholangitis) to asymptomatic liver function tests (LFT) abnormalities. Presence of biliary complication should be suspected in every case with unexpected increase in LFT (AST, ALT, gamma-GT, ALP or bilirubin); patients could also report non-specific symptoms, such as fever, fatigue, abdominal pain (right-upper quadrant) or fever. No validated diagnostic algorithm have been proposed for the investigation of suspected biliary complications, however it is widely accepted to perform trans-abdominal ultrasound (t-US) with Doppler study as first-line test, for the exclusion of hepatic artery stenosis-obstruction and evaluation of biliary tree. In the case of suspected vascular complication, a computed tomography-scan with vascular reconstruction and a therapeutic hepatic angiography have to be performed. On the other hand, the patient should undergo liver biopsy to exclude rejection or hepatitis C recurrence.

After exclusion of both vascular and parenchymal conditions that could justify the manifestation, magnetic resonance cholangio-pancreatography (MRCP) or even a cholangiogram through a T-tube are considered the diagnostic standard for biliary tract complications[9]. Invasive approaches, such as endoscopic retrograde cholangiography (ERC) or percutaneous trans-hepatic cholangiography (PTC) should be considered treatment options rather than diagnostic tools. Overall, first-line treatment approach have to be decided based on local expertise and residual biliary tree anatomy: Endoscopy (ERC) should be preferred in the case of duct-to-duct biliary reconstruction while percutaneous treatment (PTC) should be reserved to patients with Roux-en-Y choledoco-jejunostomy or after failure of endoscopic attempts. Surgery has to be considered a rescue therapy, after failure of all other treatment options. The incidence and principal risk factors for biliary complications are summarized in Table 1.

Biliary stricture

The development of stricture is the most common biliary complication after LT. Early strictures are mainly related to technical issues and observed more frequent in the case of living donor LT (2.5 folds) than deceased donor LT[10]. Late strictures, occurring usually 6-9 mo after LT, are secondary to ischemia, vascular insufficiency, immune injuries or other complications (*i.e.,* leak or cholangitis). Biliary strictures could be classified upon their anatomic localization into anastomotic strictures (AS) and non-AS (NAS).

Anastomotic strictures: AS are single, short and circumferential; AS occur usually within 1 year after LT and are more commonly observed in patients who underwent Roux-en-Y choledocho- or hepatico-jejunostomy rather than duct-to-duct reconstruction. Thus, the direct anastomosis between biliary tree and the intestinal limb expose the biliary system to the intestinal microbiota. Bile leak is (after removal of T-tube) represents another independent risk factor for the development of AS.

Clinical manifestations range from asymptomatic liver function test abnormalities to jaundice, pain or fever (in the case of cholangitis). Intrahepatic bile duct dilation could be observed on t-US, however in post-transplant setting, it is not uncommon to find a clinically significant biliary stricture without upstream dilation, due to increased periductal fibrosis. Liver biopsy could show the presence of bile duct proliferation and bilirubin deposition. MRCP or direct cholangiography (through T-tube) represent the gold standard for the diagnosis of AS.

Table 1 A detailed clinical presentation and suggested therapeutic approaches for each condition

Biliary complication	Incidence	Risk factors
Stricture		
Anastomotic	4%-12%	Ischemia, surgical complications, duct-to-duct anastomosis
Non-anastomotic	1%-10%	Hepatic artery thrombosis, cold ischemia time, immune conditions (AB0 mismatch), recurrence of underlying PSC, cytotoxic injuries (hydrophobic bile acids)
Leak or fistula	2%-25%	Surgical issues, T-tube removal
Obstruction (stone, cast, sludge, clots)	1%-6%	Stricture, kinking, infections
Cholangitis	10%	Concomitant biliary complications (stricture, obstruction) or maneuvers (ERC, PTC)
Sphincter of Oddi dysfunction	2%-7%	Efferent denervation of papillary region
Hemobilia	[1]	Endoscopic or percutaneous biliary maneuvers, liver biopsy
Compression		
Cystic duct mucocele	Rare	Mucus-producing cells in cystic duct remnant
Periductal Neurinoma	Rare	Unknown
Periductal lymphoma	Rare	Unknown (immunesuppresive therapy?)
Kinking	1.6%	Redundant donor or recipient CBD remnant
Biliary cast syndrome		Hilar stricture, untreated obstruction
Ductopenia (vanishing bile-duct syndrome)	Rare	Drugs (antibiotics, chemotherapy), chronic rejection, ischemia, untreated stricture

[1]Only case reports are available in literature. PSC: Primary sclerosing cholangitis; CBD: Common bile duct; ERC: Endoscopic retrograde cholangiography; PTC: Percutaneous trans-hepatic cholangiography.

In patients with duct-to-duct reconstruction, ERC represents the first-line treatment approach for biliary stricture, leading to successful resolution of AS in up-to 70% of patients[11-13]. After deep biliary cannulation and biliary sphincterotomy, endoscopic balloon-dilatation is able to reduce AS in a significant amount of cases; however, balloon-dilation alone is burdened by a significant rate of stricture recurrence (up to 60%); therefore, stricture dilation alone is not a reliable treatment. In the last 15 years, increasing evidences suggest that balloon dilation followed-up by biliary stenting appears to provide a more durable effect: Placing one or more 10 French plastic prosthesis reduced stricture recurrence to about 30% of cases. Stent patency ranges from 2 to 4 mo, due to presence of casts, debris and clots; it is indicated to exchange plastic stents every 3 mo for the first 9-12 mo, placing larger ones or multiple stents, until the resolution of the stenosis. We suggest evaluating the presence of residual stricture assessing the resistance to the transit of inflated balloon catheter through the anastomosis[14-18]. A recent systematic review reported a 80%-95% of stricture resolution after endoscopic placement of fully covered self-expanding metal stents (SEMS); however a study reporting the use of SEMS in patients with post-LT AS reported a significant rate of complications (up to 38%, mostly cholangitis) with worse clinical outcome (68% of stricture resolution)[19,20].

In patients with Roux-en-Y choledocho-jejunostomy the altered anatomy of the upper gastrointestinal tract the endoscopic access to the biliary tree is usually unfeasible. Some authors reported successful ERC using scope designed for the exploration of small bowel (single or double-balloon enteroscopy)[21]; however, in these patients, percutaneous approach with stricture dilation and stenting is usually performed[22,23].

Recent technical advances suggest that endoscopic ultrasound (EUS)-guided approach (*i.e.*, trans-gastric intrahepatic access) with antegrade treatments could be useful in this difficult-to-treat population[24].

In the case of failure of endoscopic approach (failure to traverse the stricture with a guidewire, refractory stricture or residual AS despite several ERC) surgical re-intervention could be considered: Resection and duct-to-duct re-anastomosing or conversion to Roux-en-Y hepatico-jejunostomy usually lead to AS resolution, eliminating the need of multiple intervention requiring hospitalization. Surgery is widely considered a second-line treatment (after failure of endoscopic or percutaneous interventions); however, in selected cases such as late tight stricture, bilioenteric anastomosis is the first-line approach in order to reduce futile intervention and to delay curative option[25].

NAS: Post-LT strictures could be localized at any level of the biliary tree. Early (within the first 12 mo) NAS have been related to chronic ischemic injuries and are more usually detected in the common bile duct, common hepatic duct or bifurcation; on the other hand, late-onset (> 12 mo) NAS are related to immunological factors and have been detected in a diffuse pattern affecting the intrahepatic small bile ducts. Overall incidence of NAS ranges from 1% to 10%[13].

Cholangiographic features are similar to those observed in patients with primary sclerosing cholangitis. The diffuse presence of multiple strictures is responsible for development of sludge deposition, casts and even acute recurrent cholangitis. Presence of NAS is associated to poor prognosis and reduced graft survival.

The goals of NAS treatments are the same of AS ones; biliary drainage and stricture dilation have to be reach through all the available non-surgical approaches (endoscopic, percutaneous, even combined). The presence of concomitant multiple strictures and the difficult localization (small intrahepatic ducts) account for the reduced treatment outcomes. Endoscopic sphincterotomy, balloon-dilation (4-6 mm, smaller than AS) and stenting (10-11.5 Fr, replaced every 3 mo) are similar approaches; patients with NAS usually require

more ERC interventions but only 50% of them achieve long-term successful clinical results[26].

Patients with extrahepatic NAS with good graft residual function could undergo surgical resection construction of a Roux-en-Y hepatico-jejunostomy. In the case of failure, up to 50% of the patients with NAS, require retransplantation[27].

Leak

Bile leakage could be observed in the early post-LT (within 3 mo) from the anastomosis, the cystic duct stump, from the insertion of the T-tube or, in the case of living donor LT or split-LT, from the cutting surface of the liver graft. Overall estimated incidence was 8.2%[26].

The mainstay of treatment of a bile leak is the reduction and decompression of biliary tree; in the case of refractory leakage, biliary drainage could be necessary to healing process. In the case of early occurrence, if the T-tube was already *in situ*, bile leak could be managed conservatively by leaving the T-tube open without further intervention. In the case of small leak, ERC with sphincterotomy is able to resolve the leakage. In the case of persistence of endoscopic sphincterotomy, placement of biliary plastic stent is able to resolve 90%-95% of early bile leaks. Usually, the biliary stent was placed with 2 mo and then removed (shorter period could not be adequate for healing process due to immunosuppressive therapy and could be justified only in the case of suspected obstruction).

In patients with Roux-en-Y anatomy, percutaneous or even surgical approach is usually necessary; we hypothesized that the decompression of the biliary tree through EUS-guided access could be an intriguing field of development for future research directions[28-30].

Biloma: Continuous bile leak within the liver or abdominal cavity could result in a uniloculated biliary collection; biloma could compress the biliary tree, vessels or could even be superinfected, leading to clinical manifestations.

Treatment: small biloma usually are self-limiting and resolve spontaneously; in complex collection, endoscopic sphincterotomy and stenting could be necessary to heal the underlying fistula. In the case of infected collection, drainage is necessary. If ERC was not sufficient to drain the biloma both percutaneous and EUS approach have been demonstrated efficacy and safe[31].

Surgical drainage has to be considered only as rescue therapy, after failure of all conservative approaches.

Biliary stones and other filling defects

Presence of biliary stones, sludge, cast, blood clots or even migrated stents could be observed in a significant amount of LT-patients (up to 10%); biliary stones are the most common filling defects observed in this setting[13].

The concomitant presence of biliary tree anatomy alterations, strictures, acute cholangitis, increased bile viscosity and stasis, drug-induced lithogenesis (*i.e.,* cyclosporine), bile acid depletion and cholesterol supersaturation are all concomitant risk factors for post-transplant CBD stones.

Endoscopic removal of CBD stone is the first-line treatment option. Stone number, size and shape, presence of impacted stones, concomitant biliary tree anatomy and presence of distal narrowing are the most common causes of ERCP failure. Moreover, in patients with previous LT, the difficult biliary access and the possible presence of concomitant biliary complications (mainly strictures) further restrict the efficacy of the interventions[32].

In patients with duct-to-duct anastomosis, the underlying presence of concomitant complications (stricture, kinking, *etc.*) should be treated accordingly. In patients with Roux-en-Y bilioenteric anastomosis, a first approach with an enteroscope, when available, should be attempted; in the case of failure, percutaneous approach is indicated. We also suggest, as future field of research, the comparison between PTC and EUS-guided biliary access, drainage and stone clearance.

In the case of difficult CBD stones (*i.e.,* large stones, triangular-shaped, or discrepancy between stone size and narrowed CBD diameter) we reported the safety and efficacy of ESWL. Among six patients with difficult choledocholithiasis, after failure of either endoscopic or percutaneous approaches, ESWL led to complete resolution of biliary complications in 5 patients (> 80%) with no procedure-related adverse events. One patients underwent surgical hepatico-jejunostomy because of tight anastomotic stricture, despite multiple endoscopic balloon-dilation and multi-stenting[32].

SOD

Papillary obstruction could be found in 2%-7% of LT patients[33]. Efferent denervation CBD remnant and ampulla but also chronic injuries with fibrotic stricture lead to hypertonic sphincter function or to obstruction. The insidious manifestation (usually characterized by elevated enzymes with or without biliary tree dilation) could justify a delayed diagnosis. Endoscopic sphincterotomy is usually effective with long-term clinical resolution. Temporary biliary stenting could be considered in the case of presence of fibrotic tissue and scarring[34].

Bile duct kinking

Redundant bile duct is defined as a reconstructed CBD (duct-to-duct anastomosis) longer than the recipient CBD creating a kinking (sigmoid-shaped loop) that, in the absence of other complications (*i.e.,* stricture), leads to cholestasis due to reduced bile outflow[35].

A single experience evaluated specifically the incidence of redundant CBD; the authors reported an incidence of 1.6%. Clinical presentation is characterized by asymptomatic cholestasis; but in our experience, presence of redundant bile duct could lead to development of CBD stones and even acute cholangitis[32].

Endoscopic stenting (long single plastic stent) lead to clinical resolution in up to 80% of patients; in the remaining, surgical Roux-en-Y hepatico-jejunostomy leads to resolution of clinical cholestasis. Also in this setting, the first-line endoscopic approach could lead to

symptoms resolution and spare unnecessary surgical intervention[35].

Recent technical and technological advances

As discussed above, minimally invasive approaches are indicated as first-line techniques for the management of biliary complications after deceased donor LT; we also discussed the possible technical difficulty encountered during deep biliary cannulation in the case of stricture, altered anatomy and other conditions in this setting. When guidewire cannot pass an angulated stenosis, the rendezvous technique can be used to overcome the issue.

The rendezvous technique is a useful and safe method for the access to biliary tree, replacement of biliary prosthesis and stent in the case of difficult biliary stricture after LT with duct-to-duct anastomosis. Various Authors reported various rendezvous techniques that could be suggested for the management of biliary complications after failure of endoscopic and percutaneous approaches[36-39].

Peroral cholangioscopy has been introduced over the past years to allow direct observation of the biliary tree and even to tissue acquisition. The introduction of new generation cholangioscopes reduced previous limitations (*i.e.,* low scope resolution, low maneuverability requiring two endoscopists, unavailable accessories) and led to the new innovative applications. Some Authors, for example, suggested the use of Spyglass for difficult biliary cannulation in the case of severe stricture and use peroral cholangioscopy to evaluate and treat anastomotic stricture after liver transplantation[40,41].

CONCLUSION

The clinical outcome of patients receiving liver transplantation could be significantly affected by biliary complications, including strictures, leaks, stones or debris, bilomas and SODs; early diagnosis and treatment of these conditions allow to markedly reduction in morbidity and mortality[42]. Therapeutic gold standard is represented by conservative approaches, both endoscopic and percutaneous, based on the type of biliary reconstruction, the local availability of the procedures and specific expertise[43]. With continuous improvements in surgical, endoscopic and echoendoscopic techniques[44], the management of biliary complications constantly evolves; what has not changed over time is the pivotal role of the early detection and management, in order to reduce the clinical burden and to improve long-term outcome (graft function and patient survival). We hope that in the next future, with the availability of new expertise, knowledge and specifically designed devices, the endoscopic management of biliary complications will further improve the quality of LT-management, with a reduction of cost related to surgery and hospitalization.

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