
Endoscopic Treatment of Biliary Complications after Liver Transplantation

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Abstract

Biliary complications remain a frequent and significant issue occurring in up to 30% of patients after liver transplantation. Their development and presentation are associated with specific transplant issues such as surgery technique, immunosuppression, rejection, damage of vascular supply, infections and disease recurrence. With the expanding and demanding surgical techniques in reduced, living related and splitting donors, the technical factors play a crucial role. Biliary complications comprise a long list of varied events corresponding to biliary problems in non-transplant conditions. The most frequent are anastomotic strictures and leaks followed by hilar (ischemic-like) and intrahepatic strictures, sphincter Oddi dysfunction, stones and stenoses due the extraluminal pressure. The diagnostic work-up and treatment involve usual modalities. The treatment of biliary complications requires a multidisciplinary approach, in which all three main options – endoscopic, radiologic and surgical – play a role. Endoscopic management is usually preferred due its comprehensiveness, efficacy and safety. Alternatively, the radiologic approach can be used particularly if there is not a comfortable transluminal access to the biliary tree. Both approaches can be combined and the success can be expected in up to 80% of patients. As in non-transplant conditions, sphincterotomy, multiple stent insertion with or without dilatation, and extraction of stones are used. The specific issues of endoscopic procedures after liver transplantation include postprocedural cholangitis prevention, consideration of coagulation disorders and sedation of patients with various mental impairments. Surgery, usually Roux-en-Y hepaticojejunostomy, is a demanding procedure potentially solving the obstruction for ever. Nevertheless, stenosis of the anastomosis and the episodes of reflux cholangitis can compromise long-term outcomes in up to 20% of patients. A universally acceptable therapeutic approach to biliary complications has not been defined, and local expertise, usually inevitably uneven, plays an important role.

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Biliary complications continue to be a significant cause of morbidity and even mortality after orthotopic liver transplantation (OLT) [1–8] (table 1). Given the generally increased patients' vulnerability after OLT, it is necessary to manage these complications promptly and effectively to prevent an irreversible liver damage and a threat to the recipient's life. Biliary complications cannot be considered as a separate issue. They often develop as a consequence of the underlying problems specifically associated with liver transplantation in patients with immunosuppression modulating clinical manifestations and laboratory findings. Not exceptionally, they can occur together with other complications such as primary disease recurrence, rejection, vascular problems or cytomegalovirus (CMV) infection. To assess the problem comprehensively and to correctly organize the management of such a complicated patient is the masterpiece of medical skill.

Table 1. Biliary complications in various surgical anastomosis techniques

Reference (first author)	Center	Year	n	Total %	Leaks %	Strictures %
<i>Duct-to-duct anastomosis</i>						
Lebeau [1]	Pittsburgh	1990	193	20	2	18
Davidson [2]	Royal Free	1999	100	31	17	14
Graziadei [3]	Innsbruck	2006	515	16	NA	16
<i>Roux-en-Y hepaticojejunostomy</i>						
Ringe [4]	Hannover	1989	84	24	12	2
Lebeau [1]	Pittsburgh	1990	187	12	9	3
<i>Living donor liver transplantation</i>						
Giacomoni [5]	Milano	2006	23	48	22	26
Wojcicki [6]	Birmingham	2006	70	26	20	4
<i>Cardiac death donors</i>						
Suarez [7]	Coruna	2008	27	42	4	
De Vera [8]	Pittsburgh	2008	141	25	NA	NA

NA = Not analyzed.

Biliary Reconstruction of Liver Transplantation

To achieve high technical success of endoscopic treatment of biliary complications, a detailed knowledge of the anatomy of biliary reconstruction as well as knowledge of specific issues of post-transplant pathophysiology is essential. Biliary reconstruction is created as the final step of OLT after vascular anastomoses. The gallbladder interposition technique was used in the pioneering years utilizing the gallbladder as the graft conduit between the donor and recipient bile ducts. In early reports by Starzl and Calne, the association of bile stasis with stone formation and cholangitis resulted in morbidity of up to 50% and mortality up to 30%, fully deserving the reference of being the ‘Achilles heel’ of this demanding surgical technique.

Nowadays, end-to-end duct-to-duct anastomosis in recipients with healthy native bile ducts of compatible caliber is the preferred technique in most centers. The resulting continuity of bile ducts most corresponding to original structure allows access to and efficient treatment of complications by standard endoscopic techniques. Similarly good results were obtained by other centers using a side-to-side variant. Occasionally and more often in the past, the reconstruction was complemented by temporary T-tube biliary drainage with two presumed aims: to visualize the bile ducts whenever needed, and to prevent anastomotic stricture. The results of several comparative studies differ but the second premise was never reliably met, and leaks prevailing in T-tube groups caused that the use of preventive drainage has been mostly abandoned [9–12].

Roux-en-Y hepaticojejunostomy is utilized in patients with bile ducts altered by the pre-existing disease such as sclerosing cholangitis. It can be also used in the presence of major disparity in size of ducts, and it is often preferred in the case of retransplantation because of inadequate recipient duct length. Roux-en-Y was also the routine reconstruction technique in the first series of living-related, reduced graft and split liver transplantation. With the growing body of knowledge of the blood supply around the biliary ducts and experience, duct-to-duct anastomosis has been increasingly constructed even if multiple anastomoses are needed [13].

Table 2. Classification of biliary complications

Intrinsic	Extrinsic
Strictures	False aneurysm
<i>Intrahepatic</i>	Cystic duct mucocele
PSC recurrence	Lymphoproliferative disease
Secondary cholangitis	Cystic duct mucocele
<i>Perihilar</i>	Chronic pancreatitis
Ischemic	Recurrent/de novo cancer
Idiopathic (ischemic-like)	
<i>Anastomotic</i>	
<i>Distal</i>	
Papillary dysfunction	
<hr/>	
Leaks	
<i>Anastomotic duct-to-duct</i>	
<i>Anastomotic HJA</i>	
<i>T-tube location</i>	
<i>Cut surface</i>	
<i>Missed segmental duct</i>	
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Stones, cast, T-tube remnant	
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Hemobilia	
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Recurrent sclerosing cholangitis	
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Cadaveric Death Brain Donors, Living Donors, and Non-Heart Beating Donors

A liver transplantation program provides full recovery from various otherwise inevitably lethal conditions (chronic end-stage liver disease, acute liver failure, selected tumors and others) in a large majority of transplanted patients. With an expansion of indications and technical progress the shortage of organs has arisen as a critical issue. Various ways have been explored to enlarge and optimally utilize the pool of donors. There are three different donor sources with specific biliary consequences: cadaveric brain donors are utilized in Europe and the USA in a large majority of cases. The advantage of the living donor technique prevailing in some Asian countries is the optimal timing of the elective procedure with a minimal time loss, which could be, on the other hand, compromised by more complicated biliary anastomoses of a reduced donor organ. Using donation after cardiac death, the relative risk of graft failure in several series was increased with the higher rate of biliary complications being one of the reasons [7, 8].

Classification and Etiology of Biliary Complications

The complex pathogenesis of biliary complications is attributable to various factors including technical reasons, ischemic damage mostly due to hepatic artery thrombosis and ischemia-reperfusion injury, immunological factors such as ABO incompatibility, CMV infection, disease recurrence in primary sclerosing cholangitis, and others [14]. The consequent cholestasis contributes to the generally increased vulnerability after liver transplantation, heavily affecting particularly the

outcome of patients with recurrent hepatitis C virus (HCV) [15]. Technical reasons for biliary complications include imperfect suture with early T-tube-related leak or anastomotic stricture, leaks from the liver surface or inadvertent bile duct injuries. Biliary complications comprise a long and varied list of events with different frequency involving both the ductal and extraluminal causes. In fact, the scale of complications corresponds to biliary problems appearing in non-transplant conditions. The difference consists in the proportions and several specific aspects [13] (table 2).

Clinical Manifestations and Diagnosis

Symptoms indicating biliary complications include fever, right upper quadrant pain, non-specific abdominal discomfort, and elevation of liver particularly cholestatic enzymes. They can rapidly proceed to the development of biliary peritonitis in large leaks, but more often they remain mild and undistinguishable from other causes of cholestasis such as HCV recurrence, and acute rejection to mention at least two other common complications. The diagnosis is based on a detailed analysis of the clinical picture, laboratory examinations, liver biopsy and imaging methods. Typically, there is absence of intrahepatic bile ducts dilatation on ultrasound particularly early after liver transplantation even above tight obstruction. The direct imaging by endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography is the final step of the diagnostic work-up, which should be preceded by magnetic resonance cholangiopancreatography (MRCP).

Specific Measurements before the Scope Is Inserted

Infection Prevention

Infection is one of major complications of ERCP occurring in about 1% of procedures overall. Several reasons can play a role. Similarly to other invasive procedures, ERCP, even though poorly documented, may cause endocarditis in high-risk patients. Infection transmitted by the contaminated scope should be completely preventable by proper use of disposable accessories and utilization of the standard technique of disinfection. Thanks to universally adopted measures, cases of endocarditis and nosocomial infection including HCV, hepatitis B, and human immunodeficiency virus related to endoscopy have been exceptional in recent series. The American Heart Association recently revised their guidelines for prophylaxis of infective endocarditis, and a crucial change regarding endoscopic procedures is that antibiotic prophylaxis solely to prevent infective endocarditis is not recommended. The exceptions are the high-risk cardiac conditions including: a prosthetic cardiac valve, history of previous infective endocarditis, cardiac transplant recipients who develop valvulopathy, patients with congenital heart disease with either unrepaired cyanosis or those repaired by prosthetic material within 6 months after the procedure, or those with a residual defect. Since the enterococci, which make part of the common bile duct flora in cholangitis, are the invading agents in endocarditis, either amoxicillin or ampicillin should be included for the antibiotic protocol for enterococcal coverage in these patients.

The most frequent cause of cholangitis after ERCP is the flare-up of infection being already present in the bile ducts. The common pathogens include *Pseudomonas aeruginosa*, *Klebsiella* spp., *E. coli*, *Bacteroides* spp., and *Enterococci*. Precipitation of the infection is caused by the elevated intraductal pressure when complete bile drainage is not achieved. To eliminate these factors, it is highly recommended to aspirate bile before contrast injection and to complete

endoscopic treatment (removal of stones, drainage of all relevant visualized strictures) within one session. Risk factors to be considered also involve jaundice, previous cholangitis, previous endoscopic treatment, combined endoscopic-percutaneous procedures, hilar tumors and primary sclerosing cholangitis because the bile duct obstruction is difficult to be relieved completely, and transplant patients on immunosuppressive regimens.

The role of antibiotic prophylaxis is controversial and a variety of practices exist. Several randomized clinical trials (RCTs) have been published showing reduction of bacteremia, but their relevance was inevitably limited due to the small number of clinical infections. No RCT has been conducted exclusively with transplant patients. For all these reasons, the general attitude to antibiotic prophylaxis is becoming more and more selective with their application in highly suspected risk-related conditions only, with transplant patients being exactly the case. ERCP should only be employed in transplant patients with highly suspected biliary obstruction and after MRCP. In fact, most of these patients are already on an antibiotic regimen due to clinical/laboratory manifestation of infection. If not, we recommend 400 mg of ciprofloxacin to be given intravenously (peroral administration is probably similarly effective) 2 h before the procedure and to continue with the administration until complete drainage is achieved. Other options involve gentamicin, cephalosporins and ureidopenicillins [16, 17].

Coagulopathy – Bleeding Disorders

ERCP and subsequent endoscopic treatment are commonly undertaken in transplant recipients with abnormal coagulation due to liver dysfunction or anticoagulation therapy. Other risk factors include thrombocytopenia (including hemodialysis-caused coagulation disorder) and initiation of anticoagulation therapy within 3 days after the invasive procedure; on the other hand, enlarging of previous sphincterotomy and the use of aspirin or non-steroidal anti-inflammatory drugs do not seem to raise the risk. Data dealing specifically with sphincterotomy in patients with liver disorders are unavailable and a commonly shared view is that coagulopathy should be managed according to rules applied to liver biopsy. Generally, there are widely divergent opinions about the values at which abnormal coagulation indexes signal a significant risk for any kind of invasive procedures including endoscopic sphincterotomy. The patient's platelet count as a part of complete blood count, and prothrombin time or international normalized ratio should be checked at a suitable juncture prior sphincterotomy. However, the utility of these tests (which are not equal) in predicting bleeding risk is uncertain and generally not sufficiently supported by scientific evidence. Probably more important than any laboratory parameters is taking a detailed medical history as to whether any bleeding episode had followed an invasive procedure in the past, and to search for any possible signs of recent bleeding. Whether the prophylactic use of blood products alters the risk of bleeding is currently unknown. Nevertheless, it is commonly assumed that platelet transfusion should be considered when the thrombocyte count is $<50,000\text{--}60,000/\text{ml}$ and, if the prothrombin time is >4 s longer (or international normalized ratio >1.6), then a transfusion of fresh-frozen plasma may bring the bleeding risk into the desired range [18]. The mixture of factors concentrates could be considered in severe coagulation disorder. The appropriate practice of endoscopic procedures on patients on anticoagulation or antiplatelet therapy is specified in detail in the guidelines of the endoscopic societies and the conditions of post-transplant care do not possess any specificity. Adoption of all these measures cannot completely eliminate the increased risk of hemorrhage in the complex bleeding disorder accompanying the liver dysfunction in the post-transplant patient. The endoscopist should avoid the use of pure cutting current and to stop actively, using local endoscopic techniques, any bleeding that may occur immediately after sphincterotomy.

Sedation and Anesthesia

During the thorough pre-transplant evaluation and post-transplant follow-up, patients are often exposed to many endoscopic procedures which could make them more anxious and less tolerant. The procedures early after transplantations or in impaired condition (ASA class IV-V-E) have to be performed with the assistance of an anesthesiologist, often under general anesthesia. The therapeutic procedures due to an abnormal anatomy of reconstructed bile ducts are often prolonged. A considerable proportion of transplant procedures are performed in alcohol abusers. Chronic alcohol use increases the dose requirements for anesthetic, sedative or analgesic agents. This is thought to be because in part of enzyme (particularly cytochrome P450 2E1) induction, or through the development of cross-tolerance. The effective doses of propofol, opioids and other drugs are increased, the patients may become paradoxically agitated, uneasily controlled and less tolerant to any disturbing procedures. The increased requirements for anesthetics may exacerbate the risk of cardiovascular instability in patients suffering from cardiomyopathy, and increase the risk of adverse effects of all kinds. All these consequences make the endoscopic procedures particularly demanding. The administered drugs have to be precisely titrated and the patient adequately monitored. The participation of an anesthesiologist on presumably risk-associated procedures is highly recommended [19].

Biliary Complications after Liver Transplantation – Specific Issues and Their Management

Basically, treatment of biliary complications does not differ from the treatment of the identical structural entities and its techniques have been repeatedly described in detail and are more or less standardized. Nevertheless, there are several specific features which have to be considered to avoid an unexpected surprise and to achieve optimal results. Since few data from well-designed prospective trials are available, the specific techniques and tricks described below are based besides a search of the literature on the continuous experience with more than 700 liver transplantations and management of approximately 200 biliary complications being followed in the single department. This has made it possible to follow the results of treatment from both immediately and in the long run and to discuss all individual aspects with representatives of other specialties participating on the transplantation program such as invasive radiologists, surgeons and transplant hepatologists. A retrospective analysis of the first 500 consecutive primary transplant procedures revealed biliary complications in 147 (29.4%) patients. Choledochocholedochal anastomotic stricture was found in 90 patients, and leak in 38 patients. The scale of other less frequent complications included non-anastomotic hilar (ischemic-like) strictures, strictures due to post-transplant lymphoproliferative disorder, choledocholithiasis and papillary stenosis. Endoscopic treatment was fully successful in 88 out of the 117 (75.2%) patients with anastomotic strictures or leaks. Retransplantation rate was higher in patients with than in those without biliary complications (10.9 vs. 5%). The occurrence of biliary strictures did not have any effect on mortality. We have learnt that, in transplantology more than in non-transplant medicine, every patient is a unique complex entity, and that clinical decision-making should be, as a rule, preceded by a detailed analysis of the patient's condition and a careful evaluation of all available, usually unequally established techniques, skill and experience.

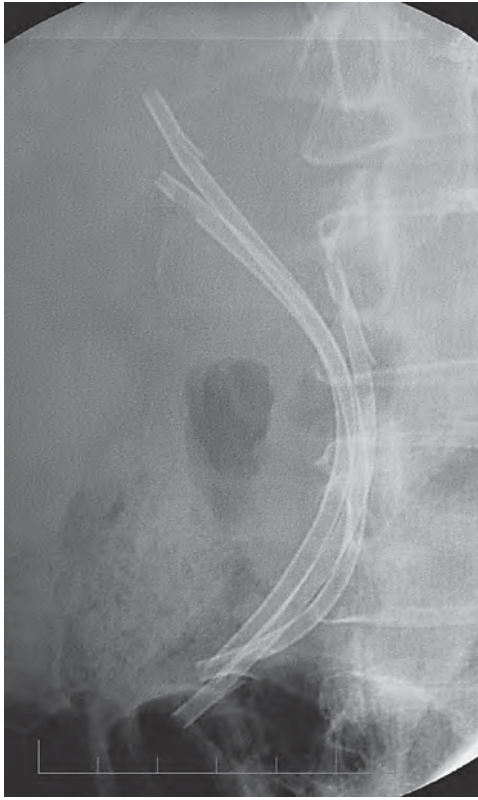
Endoscopic Sphincterotomy

The technique itself does not differ from the sphincterotomy performed in other patients. Nevertheless, the spontaneous motility of the bile duct is abolished due to the surgical

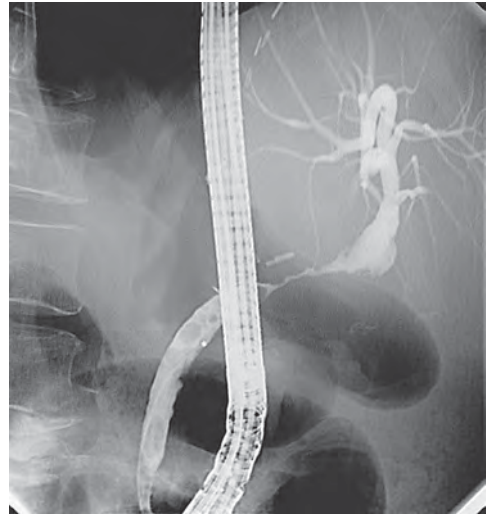
reconstruction resulting in the denervation of the biliary tree. Therefore, evacuation of the contrast material cannot serve as a reliable parameter of bile duct function, and cholestasis tends to occur after sphincterotomy of a standard size which would be otherwise fully sufficient for what it is aimed – stent insertion or bile duct stones extraction in a non-transplant condition. As a result, we always recommend to perform the sphincterotomy to the maximum possible (safe) extent.

Anastomotic Strictures

Anastomotic strictures, being, together with leaks, the most common post-transplant biliary complication, are highly specific and almost unparalleled to non-transplant conditions. They are often asymmetrical with the shape which can be difficult to precisely project on x-ray due to overlap with one or two cystic stumps. The shape of a prolonged reconstructed bile duct in the anastomotic area may resemble letter 'S'. For the irregular lumen of the anastomosis with cystic stumps, it may be exceptionally quite difficult to pass the guidewire through the stricture. Often, several types of wire with different properties concerning the diameter, flexibility/rigidity and slipperiness have to be tried. The direction of the tip of the wire can be enhanced by the use of an angled tip, sphincterotome or balloon catheter. The stricture can be dilated by balloon before stenting, but we do not find it necessary if planning to insert a single stent. The strategic principle is that a benign anastomotic stricture unlike a malignant stenosis does not need to be bridged only, but the lumen of the bile duct has to be fully reconstituted to respond to normal anatomy, and therefore, multiple stents according to the size of the bile ducts below and above the stricture have to be inserted. Both basic techniques of multiple stent insertion can be used: two wires prior to inserting either stent, or to insert the wire along and after the first stent insertion. The optimal number and position of multiple stents is usually achieved in several sessions separated by short 1- or 2-week intervals. Even if, in our opinion, stenting should be the preferred technique, there are several studies showing that simple balloon dilation without stenting relieves the stricture with similar success, and even with reduced complication rates. It seems that the chance for the optimal remodeling of the anastomosis and the stricture is higher early after transplantation and lower later on, if a firm fibrotic stricture has already developed. If the reconstructed bile duct after liver transplantation is prolonged with the S shape, we select a longer stent that can be estimated from the distance between the stricture and duodenum. The reason is that the stent passing through the S-shaped bile duct creates friction making the insertion more difficult. If the stent is not long enough, its end may become impacted in the orifice of the stricture, which makes it impossible to go through. On the other hand, when a curved stricture is overcome, the shape straightens and this can expel the proximal end of the stent far above the stricture, possibly above the hilar junction. This unfavorable position of the proximal end can hardly be prevented. One stent alone inserted into S-shaped bile duct with anastomotic stricture may adopt the curvature of the duct, while multiple stents straighten it, which is the optimal outcome. If the first one or two inserted stents are located with their proximal ends far above the stricture, the length of the third stent should be shorter to drain the bile from various levels of the bile ducts to avoid cholestasis and debris accumulation above the stricture. A firm S-shaped bile duct can expel the stent back to the duodenum with the risk of duodenal perforation by the stent on the opposite side to the orifice. More stents inserted in parallel make the expulsion less probable. The stents should be exchanged regularly at 3-month intervals as recommended elsewhere, and are usually removed after an interval of 6 months to 1 year. If there is a failure of endoscopic access, the transhepatic approach follows. The first plastic stent can be inserted either transhepatically or using the rendezvous technique transpapillary [20–22] (fig. 1–3).



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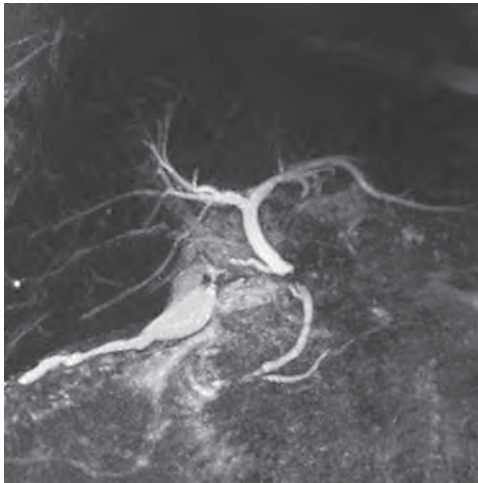
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Fig. 1. Multiple plastic stents.

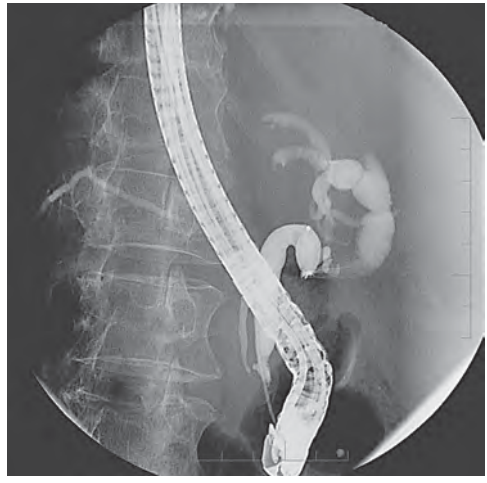
Fig. 2. Hilar ischemic-like stricture.

Fig. 3. Anastomotic stricture on MRCP.

Fig. 4. S-shaped reconstructed bile duct.



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Non-Anastomotic Hilar Strictures (Ischemic-Type Biliary Lesions)

With an incidence ranging between 5 and 15%, these biliary complications remain, more than anastomotic strictures, a substantial source of morbidity, graft loss and even mortality after liver transplantation. Their multifactorial origin embraces a variety of events (risk factors) including ischemia due to hepatic artery thrombosis or prolonged cold and warm ischemia, use of

University of Wisconsin solution vs. histidine tryptophan ketoglutarate, ABO incompatibility, extramural pressure by lymph nodes or tumor, original disease recurrence, or it remains obscure. The altered bile composition with the significantly lower phospholipids/bile salts ratio after liver transplantation and graft steatosis may likewise contribute to their pathogenesis [23, 24]. Endoscopic treatment consists of stent insertion similar to that in non-transplant patients, but detailed exploration and management of underlying conditions is essential. If the stricture involves segmental branches, multiple stent bridging the strictures of all ducts are necessary. In specific conditions of malignant stricture, metallic stent insertion according to commonly shared rules is the choice. Full success of the endoscopic treatment is less probable due to the location distant to the papilla making the endoscopic manipulation less effective, and due to various underlying conditions, with different outcomes. The endoscopic treatment can be combined with the transhepatic approach, if necessary [25] (fig. 4).

Intrahepatic Strictures

They are not unequivocally classified against non-anastomotic hilar ischemic-type biliary lesions, and the pathogenesis involves identical principles. Lee et al. [26] classified intrahepatic stenoses into four groups: unilateral focal, confluence, bilateral multifocal, and diffuse. The success of either non-surgical endoscopic or transhepatic interventions is inversely related to the extent of the duct involvement with the frequent need of early retransplantation [26].

Distal Strictures

The strictures below the anastomosis are usually caused by chronic pancreatitis. Surprisingly, pancreatitis is often asymptomatic and cholestasis is the only manifestation of advanced pancreatic disease. Other causes involve extramural pressure by malignancies, mucocele, and biloma. They can be managed similarly to non-transplant conditions [13, 25].

Papillary Stenosis (Sphincter of Oddi Dysfunction – SOD)

Data concerning the occurrence of papillary stenosis/dysfunction after liver transplantation are less consistent compared to other specific and well-defined biliary complications (anastomotic strictures, leaks). Cholestasis was observed in 3–7% of patients following T-tube clamping early after liver transplantation but, according to some authorities, it seems to be transient and self-limited. Papillary stenosis can be facilitated or unmasked by liver transplantation since the abolished bile duct spontaneous motility by ducts reconstruction and denervation. On the other hand, the fact that some patients develop SOD and others do not while undergoing the same surgical technique, is intriguing [13, 25, 27]. The embarrassment and inevitable diversity of approaches can be demonstrated on a model case: A patient developed significant cholestasis several months after liver transplantation. Liver biopsy excluded other causes, sonography and MRCP have shown dilatation of the recipient choledochus, which was confirmed by ERCP. Multiple acceptable choices included: either to perform manometry or sphincterotomy immediately without manometry, or to wait for possible spontaneous resolution or, perhaps, to insert a stent and wait – if the cholestasis has resolved, the patient can be either followed only and, if reappearing, it would pose a strong argument for sphincterotomy. If sphincterotomy is the choice, the cut of maximal safe extent is recommended.

Bile Duct Stones

Bile duct stones are less frequent compared to leaks and anastomotic strictures, but still relatively common complication after liver transplantation. Two basic categories of choledocholithiasis

can be classified: Sludge or small stones usually develop as a late complication. Soft pigmented composition prevails suggesting that cholestasis and infection play a decisive role. Cholesterol supersaturation and related changes in lithogenicity are probably less important. The occurrence of stones is often associated with biliary strictures. More rarely, extensive casts completely filling the biliary tree have been described. Casts usually appear relatively early after liver transplantation due to prolonged ischemia resulting in severe diffuse biliary mucosal damage and defoliation. Endoscopic treatment responding to non-transplant conditions should be preferred to be followed alternatively by the transhepatic approach or surgery in the event of failure. Nevertheless, the long-term outcome reflecting the underlying conditions can be limited when multiple stones or cast with diffuse bile duct damage occur [13, 25, 28, 29].

Port-Transplant Lymphoproliferative Disorder

Port-transplant lymphoproliferative disorder is a serious and complex clinicopathologic disorder that has been related to several specific factors, particularly overimmunosuppression and viral infection. The rate of post-transplant lymphoproliferative disorder is close to 3.0%. The early cases are located in the liver hilum causing biliary stenosis with cholestasis. The treatment is based on several principles. The degree of immunosuppression should be reduced. Antiviral drugs have been used mostly in children. Chemotherapy has been used in the presence Epstein-Barr Virus-negative monoclonal lymphomas developing with delay after transplantation. Other options involve rituximab, a chimeric anti-CD20 antibody, radiotherapy and interferon- α . The local biliary involvement can be relieved by stent insertion from either the endoscopic or transhepatic approach or, exceptionally, by surgery. Endoscopic treatment is consistent with the endoscopic approach to hilar strictures of other causes with commonly required transhepatic assistance. Survival is determined by the pathobiology of the PTDL with a worse prognosis in early disease similar to the prognosis of other post-transplant malignancies [30].

Bile Leaks

Bile leaks have been reported in 1–25% of OLTs performed. They can be divided into early, defined by a time period of 1–3 months after OLT, and late leaks. Anastomotic leaks are related to technically insufficient suture, or to ischemic damage, usually to the donor bile duct. Other risk factors considered include recipient and donor age and the MELD score [31]. They seem to be unrelated to the type of biliary duct-to-duct reconstruction. According to a recent RCT, end-to-end versus side-to-side choledochocholedochostomy did not reveal a significant difference in terms of the occurrence of biliary complications [29]. Early leakage may develop at the T-tube insertion site any time but typically after T-tube removal, in up to 30% of procedures [32, 33]. Other sites of leak comprise surface leaks and leaks from inadvertent bile ducts usually after graft reduction. The leaks can be treated either by stent or nasobiliary drainage insertion (after sphincterotomy). In small leaks, sphincterotomy alone may be sufficient (fig. 5).

Roux-en-Y Anastomosis

Several small studies were focused on endoscopic management of patients with Roux-en-Y anastomosis, which in the past could be managed with either a standard duodenoscope, gastroscope or pediatric colonoscope with limited success only. Both with double- or single-balloon enteroscope, ERCP is a feasible option with a high success rate. Limitations of this technique include the time requirements (1–2 h), and the relatively narrow scale of accessories [34].

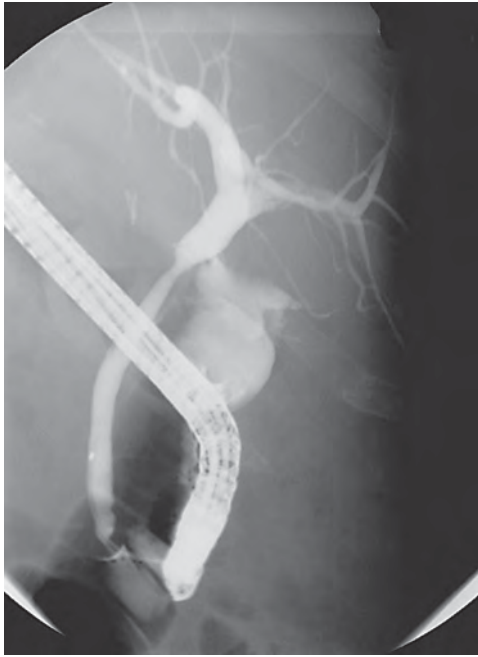


Fig. 5. Anastomotic leak. **Fig. 6.** Covered metallic stent.

Metallic Stents

The first bare self-expanding metallic stents have been shown to maintain patency longer than plastic ones in malignant strictures. Nevertheless, in benign strictures, they were mostly rejected due to failure related to mucosal hyperplasia and the fact they could not be removed. The mostly welcome feature of the metallic stents is the single-session treatment, with an additional advantage of (semi)covered metallic stents in benign strictures being they prevent tissue ingrowth and thus ensure removability using the snare or rat-tooth technique [35, 36]. Several studies have shown the potential of (semi)covered metallic stents to offer high efficacy and recurrence while keeping complication rates on an acceptable level. Comparative studies with conventional plastic stents are warranted to evaluate also the various radial forces, traumatic ends and, perhaps, also resorbable material (fig. 6).

Conclusion

The high rate and wide range of biliary complications after liver transplantation remain a challenging issue. The advent of new strategies and techniques, such as split- or reduced-size liver, living related liver transplantation, and non-heart beating donors comprising new technical and pathogenetical principles will maintain the rate of complications on a significant level. Management has to arise from individual assessment of the patient with their unique complexity comprising the morphology of the lesion, presumed pathogenesis, comorbidity, prior surgery and the patient's own preferences. Analyses that consider all these factors should determine the strategy that may offer optimal benefit for the patient. The management of biliary complications

requires a multidisciplinary approach, in which all three main options – endoscopic, radiologic and surgical – have to be weighed up one against each other. Generally, endoscopic management has to be considered in the majority of patients as the first therapeutic option due its comprehensiveness, efficacy and safety. Alternatively, the radiologic approach can be used in the majority of complications, preferably if there is not a comfortable transluminal access to the biliary tree. Proper stent placement using x-ray alone is more difficult to control, and multiple stents usually cannot be inserted [37]. Both approaches can be combined. The disadvantage of these methods is the need for multiple sessions annoying the patient and increasing the risk of complications. Surgery, usually Roux-en-Y anastomosis, is a demanding technique potentially solving the obstruction for ever. Nevertheless, obstruction of the anastomosis and the episodes of reflux cholangitis can compromise long-term outcomes in up to 20% of patients [38]. A standard therapeutic approach to biliary complications has not been uniformly defined, and local expertise, usually inevitably uneven, plays an important role. The same biliary complication, e.g. extrahepatic stricture, can be (and used to be) treated by either endoscopy, or interventional radiology, or surgery, without a significant difference in the outcome among the studies. Direct comparative studies are scanty and it is not realistic to expect a well-designed prospective trial, even in the future [39]. The diverse nature of the complications requires usual endoscopic techniques of treatment and, the same as in non-transplant conditions, sphincterotomy, stent insertion with or without dilatation, and extraction of stones are the principal steps. With the advent of new technologies, such as metallic (semi)covered stents and balloon enteroscopes, the range of options will expand. The specific issues of endoscopic procedures after liver transplantation include post-procedural cholangitis prevention, consideration of coagulation disorders and sedation of patients with various mental impairments.

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