Interventional Radiology: Management of Biliary Complications of Liver Transplantation

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ABSTRACT

Major advances in the field of liver transplantation have led to an increase in both graft and patient survival rates. Despite increased graft survival rate, biliary complications lead to significant postoperative morbidity and even mortality. A multidisciplinary approach to these complications is critical. As part of the team approach, less invasive techniques used by the interventional radiologist have an increasing role in the management of complications after liver transplantation. This paper will review the current role of the interventionalist in management of biliary complications.

KEYWORDS: Liver transplantation, biliary complications, biliary strictures, biliary leak, interventional radiology

Objectives: Upon completion of this article, the reader should be able to (1) understand the factors involved in biliary complications, (2) understand how to diagnose bile leak and biliary strictures, and (3) understand interventional approaches in treatment of biliary complications.

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Few areas in surgery can match the major advances made in liver transplantation over the last two decades. This has led to dramatic increases in both patient and graft survival rates. However, despite improvements in surgical techniques, graft preservation, immunosuppressive therapy, and medical management, biliary tract complications still occur in many patients after liver transplantation and are responsible for significant postoperative morbidity and mortality. The reported biliary complication rate in some of the larger series varies from 6 to 30%.¹⁻²³ The range represents differences in orthotopic liver transplantation (OLT)

versus living donor liver transplantation (LDLT), varying surgical techniques for creating the anastomoses, and varying diligence of physicians to pursue detection. Some early series reported biliary complications in as many as 60% of the patients receiving LDLT. However, most of these series involved the pediatric population, and more recent series of LDLT in adults, using modified techniques, report a complication rate closer to that of OLT. Improvements in patient management, diagnostic tools that help differentiate biliary complications from other causes of increasing liver enzymes, and early intervention have helped decrease their impact on

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mortality. However, the morbidity remains high^{1,3,8,19,24,25} and may result in graft loss in 3 to 12% of transplant recipients, depending on the type of ductal anastomosis and the expertise of the transplant team.^{1,3,15,16,26} As the demand for liver transplantation increases and as nonsurgical interventions become the first-line treatments in biliary complications, interventional radiologists are playing an increasingly vital role in the long-term care of transplant recipients.

HISTORICAL CONSIDERATIONS

Biliary duct reconstruction at transplantation has undergone several modifications over the past 25 years. Early techniques involved creation of a cholecystoduodenostomy or a Roux-en-Y cholecystojejunostomy with preservation of a component of blood supply to the donor bile duct from vascular plexuses fed by the cystic artery. Biliary obstruction, frequently at the level of the cystic duct, led to the use of a choledochocholecystocholedochostomy to reestablish the biliary conduit. This method also allowed an intact sphincter of Oddi, reducing the risk of ascending cholangitis. Although the incidence of biliary ischemia and leaks decreased with this procedure, the rate of anastomotic strictures causing biliary obstruction and infection increased. Subsequent modifications in technique led to the creation of choledochocholedochostomy (duct-to-duct) and choledochojejunostomy (duct-to-jejunum), which resulted in better performance, and to these techniques becoming the standard in most centers.²⁷⁻³³

FACTORS RESULTING IN BILIARY COMPLICATIONS

Ischemia and Ischemic-Type Injuries

To understand ischemic injuries, it is important to understand the blood supply to the biliary tree. Northover and Terblanche^{34,35} were able to define the vascular anatomy supplying the biliary ducts at various levels. Bridging collaterals between the branches of the right and the left hepatic arteries along the inferior surface of the hepatic hilum form the hilar plexus. Marginal arteries arise from the posterior-superior pancreaticoduodenal artery; ascend along the lateral, medial and posterior margins of the common bile duct and the common hepatic duct; and terminate in the hilar plexus. From above, branches from the right hepatic artery form an arterial plexus around the right hepatic duct and branches from the left hepatic artery form an arterial plexus around the left hepatic duct that is continuous with the hilar plexus at the confluence and with the vessels around the common bile duct.^{36,37}

In whole liver transplantation, the donor common bile duct is well vascularized by the arterial plexus and

the marginal arteries via the downward flow from the left and the right hepatic arteries, protecting the common duct.³⁶ In split liver transplantation (SLT), preservation of the hilar plexus and avoidance of circumferential dissection around the left hepatic duct are crucial to prevent interference with its blood supply. As disruption or modification of the blood supply may make the extrahepatic ducts more vulnerable to necrosis, leaks, and strictures after transplantation, careful dissection is very important in both OLT and LDLT. On the other hand, the intrahepatic biliary system in a transplanted liver depends solely on the patency of the hepatic artery. Although a thrombosed or a stenotic artery usually results in global graft ischemia and dysfunction, occasionally it may be manifest as a biliary leak or stricture.^{8,19,25,32,35,38-41} Therefore, it is essential to confirm the patency of hepatic artery, especially in cases with proximal or intrahepatic biliary tree involvement. In some cases, an ischemic type of injury has been observed in the presence of a grossly normal vascular supply.⁴²⁻⁴⁵ Because these resemble biliary tract changes observed in cases of ischemic biliary damage, they are referred to as ischemic-type injuries. These changes can affect both the extrahepatic and intrahepatic bile ducts and may be associated with the formation of biliary casts or stones.^{42,46} Microcirculatory injury, low-flow states, prolonged cold ischemia times, and immunologic causes have been implicated, but the exact pathogenesis is not known.^{25,32,40,43-45,47-49}

Type of Biliary Anastomosis and the Use of T-Tubes

Currently, choledochocholedochostomy (duct-to-duct) and choledochojejunostomy (duct-to jejunum) are the two standard biliary reconstruction procedures. If the donor and recipient ducts are of similar diameter and are sufficiently long, choledochocholedochostomy is the preferred method of reconstruction in OLT and in selected LDLT candidates. This procedure is less complicated to perform and makes use of a well-vascularized recipient bile duct with an intact sphincter of Oddi to reduce enteric reflux.^{3,12,16,33,50} The reported complication rate in most large series is 7 to 20%.^{2,3,9,13,14,17,51,52} The use of T-tubes at the time of constructing a duct-to-duct anastomosis has been controversial. Proponents claim that T-tubes facilitate postoperative cholangiograms, reduce the incidence of anastomotic strictures due to the splinting, and delay the presentation of complications beyond the immediate post-transplantation period, which is thought to be an advantage by some investigators.¹⁴ However, there are some large studies that demonstrate a higher incidence of morbidity directly related to the T-tube including leaks from the exit site after removal (Fig. 1), biliary sludge, and T-tube limb migration without any potential benefit. In short,

Figure 1 Patient 2 months after liver transplantation. Three days prior to this study, the T-tube was removed after a cholangiogram (normal) but without performing a pullback tractogram. Patient presents with peritoneal signs with suspected bile peritonitis. In this image a Berenstein catheter is placed in the tract and a tractogram is performed. It shows a patent tract and a leak into the peritoneum. This was treated percutaneously with ultrasound guided drainage of an infected biloma and a catheter placed in the tract but outside the common bile duct to allow a seal (not shown).

the decision to use T-tubes depends on the preference of the transplant surgeon.^{41,54,59}

A Roux-en-Y choledochojejunostomy or a hepaticojejunostomy is used in patients receiving SLT and LDLT when there is a significant difference in the size of the donor and recipient ducts or when there are multiple biliary orifices for anastomosis. Besides LDLT and SLT, a hepaticojejunostomy is used in patients with primary or secondary bile duct disease and in retransplantation or previously surgically scarred porta hepatis. However, choledochocholedochostomy (duct-to-duct) is emerging as the anastomosis of choice (barring size disparities in the donor and recipient ducts) in both OLT and LDLT to maintain physiological biliary-enteric continuity. The data comparing hepaticojejunostomy or choledochojejunostomy with choledochocholedochostomy are sparse. Many authors believe that the incidence of biliary complications is higher in patients with a hepaticojejunostomy. The incidence of bile leaks does not significantly differ when the two anastomoses are compared,^{3,58,60,61} but the incidence of strictures seems to be significantly higher in patients with a hepaticojejunostomy.^{3,20,29,32,40,58,60,62}

Type of Graft and Related Issues

By comparison with OLT, complication rates (from bile leaks and strictures) are higher with LDLT^{11,60,62} (as

high as 35% in certain series).²⁷ The biliary leaks reported in LDLT are from the cut surface and at the site of the anastomosis and the incidence ranges from 10 to 25%.^{11,60,63} The incidence of strictures ranges from 8 to 35%.^{10,11,29,60,63–66} With further refinement in technique and with careful selection of patients, the rate of complications has decreased and LDLT is being increasingly utilized to overcome the shortage of grafts.

Besides ischemia and technical challenges, other etiologies have also been implicated in the pathogenesis of biliary strictures. Preservation of the liver beyond 12 hours may result in a higher incidence of diffuse or nonanastomotic strictures.^{8,25,32,40,67,68} Sanchez-Urdazpal et al found that a preservation time of less than 11.5 hours resulted in less than 2% biliary complications and a preservation time greater than 11.5 hours was accompanied by a 35% complication rate.⁴⁵ Others have not observed as high an incidence with prolonged preservation, suggesting differences in allograft procurement techniques.^{13,24,41,69,70} A pretransplantation diagnosis of primary sclerosing cholangitis (PSC) has also been associated with post-transplantation biliary complications.^{23–25,40,68}

Infection

In patients with bacterial, viral, and fungal cholangitis, infection can result in direct biliary epithelial toxicity and damage. Cytomegalovirus (CMV), *Candida*, and *Cryptococcus* have been implicated; although whether infection (especially CMV) is more common in these patients because they are generally more debilitated or whether it predisposes the patient to biliary strictures is unknown.^{71,72} Pre-OLT status, age, United Network for Organ Sharing (UNOS) status, and indication for transplantation seem to have no direct correlation with the incidence and type of biliary complication.^{40,58,73} Other major causes of impaired biliary drainage include biliary casts and stones, ampulla of Vater dysfunction, and external compression of the bile duct by a cystic duct mucocele.

DIAGNOSIS OF BILIARY COMPLICATIONS

The incidence of biliary complications is highest in the first few months after transplantation.^{3,6,8,24} In a study published by Greif et al, 1792 consecutive patients were observed after liver transplantation. Over one third of the patients with biliary complications were diagnosed within a month of transplantation and 80% were diagnosed within 6 months. The most common complications are biliary leaks and strictures.^{1,3,6,8,9,74} In general, biliary leaks arise early^{3,9,16,58} and strictures tend to occur later.^{3,6,8,15,16,41,75} The period during which strictures are detected is variable because of the multifactorial

pathogenesis and different detection protocols. Generally, 1 year after the transplantation, the incidence of biliary complications is low (<4% per year).³

Biliary complications often have an insidious onset with vague abdominal pain and fever. Some patients may present with asymptomatic progressive cholestasis and an increase in serum alkaline phosphatase levels. Cholangitis may be the first sign, and the differential diagnosis should include rejection, drug-induced cholestasis, viral hepatitis, and recurrence of the original disease. If cellular rejection is absent, a cholestatic pattern with persistent elevation in enzymes after T-tube capping warrants a search for biliary pathology. When a biliary cause is suspected, the work-up includes imaging studies (Doppler ultrasonography or magnetic resonance imaging) of the liver, biliary tree, and hepatic artery. Hepatic artery thrombosis (HAT) or stenosis must be ruled out. If required, an arteriogram with hemodynamic measurements should be used as a problem-solving tool.

Liver biopsies obtained either percutaneously or by a transjugular approach may provide clues, but these too are often nonspecific.⁷⁶ Findings suggestive of large bile duct obstruction include portal edema, proliferation of ducts, neutrophilic cholangitis, and hepatocanicular cholestasis. Campbell et al compared histologic findings in patients with and without strictures and found "cholangitis" to be the only histologic feature significantly associated with documented stricture.⁴⁰ Magnetic resonance cholangiography is emerging as a promising tool. However, results and yield vary from institution to institution.^{1,7,65,77,78} Because of its noninvasive nature, it is frequently used as a diagnostic test before resorting to the more invasive contrast cholangiography. In certain patients contrast cholangiography may be the only way to determine anatomic abnormalities as well as biliary sludge and cholelithiasis. In patients with duct-to-duct reconstruction, a cholangiogram may be performed by endoscopic retrograde cholangiopancreatography (ERCP). In patients with duct-to-jejunum anastomosis and in patients with incomplete ductal filling on ERCP, percutaneous transhepatic cholangiography (PTC) may be required. A cholangiogram is simple to obtain in patients with an existing T-tube and, as noted earlier, has been one of the arguments for its placement. Because patients with biliary obstruction are susceptible to infection and sepsis, all cholangiograms should be preceded with antibiotic prophylaxis against enteric pathogens to reduce the risk of septic complications. Other diagnostic tools, such as biliary scintigraphy and computed tomography (CT),⁶⁵ have limited utility in diagnosing obstruction but are useful in detecting leaks and bilomas.⁷⁹ Ultrasonography has slightly greater diagnostic sensitivity than CT for detecting biliary sludge and stones; however, overall results of both modalities have been disappointing.^{65,80,81}

BILE LEAKS AND BILOMAS

Common causes of a bile leak include anastomotic leaks related to duct ischemia and necrosis or technical imperfections and a leak from the T-tube exit site. Ischemia and necrosis at the anastomotic site usually cause early bile leaks and are often detected in the peritransplantation period.⁸² On the other hand, many late leaks are related to T-tube removal. Anastomotic leaks due to complicated reconstruction as well as the cut surface are the leading causes of bile leaks in LDLT and in patients with a choledochojejunostomy, with the reported incidence ranging from 9 to 25%.^{11,60,63,64,83} On the other hand, in choledochocholedochostomies constructed over a T-tube, the T-tube is the leading cause of leaks in 10 to 22% of the patients^{20,29,53,56,57,58,83} compared with 3 to 13% in patients without a T-tube.^{3,55,56} Both types of leaks as well as associated bilomas can be recognized on scintigraphy as well as cholangiography. Many surgeons now have either abandoned the practice of placing a T-tube or elected to prolong T-tube stenting for several months to allow tract maturation. However, after transplantation, maturation of the tract is often delayed because of immunosuppressive therapy, and despite delaying T-tube removal, Popescu et al reported a 7% incidence of bile leak (Fig. 1) with an average of 118 days to onset.⁵ When the leak is discovered after the T-tube has been removed, a sheath can be left outside the bile duct to drain the leaked bile. The sheath may be slowly backed out, allowing the tract to seal, preventing further bile leakage. Most small T-tube leaks heal spontaneously and do not require any additional treatment. Both endoscopic stenting (including nasobiliary stent placement) and percutaneous transhepatic biliary drainage can also be used to provide a "pathway of least resistance" to divert the bile, allowing most bilomas to resolve and biliary leaks to heal. With a choledochojejunostomy, endoscopic visualization is often limited, necessitating percutaneous transhepatic or transjejunal approaches. These approaches have success rates in the range of 70 to 80% for treatment of bile leaks.^{1,6,61,64}

Anastomotic leaks may result from technical causes such as unsatisfactory ductal anastomosis, tension on the anastomosis, or excessive dissection around the periductal tissue during organ procurement.^{2,58,64} They often require surgical revision,^{58,64,83,84,86} emphasizing the need for surgical finesse. These leaks occur early, often in the peritransplantation period. In centers where T-tubes are used, a cholangiogram (using gravity method) through the T-tube is obtained at 1 to 2 weeks after transplantation and is repeated at 6 weeks and 3 months with particular attention to the anastomosis. An attempt can be made to treat an anastomotic leak with an internal or external drain or a plastic stent (placed percutaneously or endoscopically) across the disrupted anastomosis to allow healing around the drain. This may be successful in minor disruptions and small leaks;

however, a severely disrupted anastomosis can be a challenge. In this case, a surgical revision may be the safest path and should be conducted expeditiously to save the graft.^{7,20,58,83,84,86}

BILIARY STRICTURES

The etiology of biliary strictures is multifactorial. These factors include ischemic or ischemic-type injuries to the bile ducts, technical problems during reconstruction of the biliary tree, cold ischemia time, and immunological factors. Biliary strictures account for approximately one half to two thirds of biliary complications in liver transplants.^{1,8,23} The incidence of biliary strictures after OLT is ~4 to 15%.^{1,3,4,9,13,14,17,20,21,24,32,40,55,58,68,87-89} In comparison, the incidence of strictures is slightly higher in LDLT, ranging from 8 to 35%.^{10,11,29,60,63,64,90} Approximately two thirds to three fourths of all biliary strictures are anastomotic.^{1,9,20,22,32,91,92} The remainder, termed "nonanastomotic," are in hilar ducts, intrahepatic ducts, or the distal recipient duct.^{22,24,32,40,91} Several authors have demonstrated a higher rate of strictures in patients with a hepaticojejunostomy.^{1,3,20,29,40,58,60} According to some investigators, both nonanastomotic^{1,3,40} and anastomotic stricture incidence is higher in patients with a choledochojejunostomy or a hepaticojejunostomy,^{20,29,32} but it has been a matter of debate.^{4,45,61}

Differentiation of anastomotic from nonanastomotic (hilar or intrahepatic) stricture is important for management and prognosis. Anastomotic strictures result from fibrotic healing and are often amenable to nonsurgical techniques, whereas the more complex non-

anastomotic strictures (hilar and intrahepatic) carry a less favorable prognosis because of underlying graft injury.^{1,8,19,23,25,40,45,68,93,94} They often do not respond to nonsurgical techniques, necessitating surgery. If the injury is severe with diffuse involvement of the biliary system, the graft survival is poor and retransplantation is often required.^{8,25}

The various factors (discussed previously) resulting in biliary strictures cause both epithelial and vascular damage leading to reduced healing because of a poor nutrient and oxygen supply. If a biliary stricture is identified as the source of cholestasis, the overall performance status of the patient, the degree of graft dysfunction, and the nature of the problem should be considered before deciding on the therapeutic modality. With improving interventional technology and techniques, management of these patients is shifting in favor of nonsurgical techniques, reflecting the belief that a multidisciplinary approach is best for the patient. Poor prognostic factors include chronic ductopenic rejection, arterial thrombosis, and a pretransplantation diagnosis of PSC. It is important to understand, however, that a surgical solution should not be delayed if nonsurgical approaches fail.

Anastomotic Strictures

Anastomotic biliary strictures are the commonest biliary complication after liver transplantation and account for two thirds to three quarters of all biliary strictures.^{1,9,20,22,32,91,92} (Fig. 2) They are often the result of fibrotic healing^{1,9} and typically arise later than biliary leaks and nonanastomotic strictures. In most major

Figure 2 (A) There is an obvious stricture in the common hepatic duct, at the anastomotic site. This site has been dilated to 7 mm and stented with 20 French stent for 6 months. However, this over-the-wire cholangiogram shows no significant improvement. (B) Repeated angioplasty with an additional 6 months of stenting showed marked cholangiographic improvement. However, the patient did not tolerate the clinical testing for 2 weeks, implying functional obstruction. The next option for the patient would be surgical revision.

medical centers nonsurgical treatment has become the first line of intervention in anastomotic strictures. Although these strictures often require two to three procedures, they respond well to nonsurgical approaches and the success rate is in the range of 75 to 85%.^{1,4,19,21,26,41,92} With nonsurgical interventions, surgery can be avoided in many patients and only 10 to 30% of these patients require reexploration or conversion to a choledochojejunostomy or hepaticojejunostomy.^{1,4,7,15,21,26,58,60,89}

In patients with duct-to-duct reconstruction, endoscopic treatment is the modality of choice. The stricture can be visualized in over 90% of patients and therapeutic success (crossing the stricture, balloon dilatation with or without stent placement) is achieved in 30 to 75%. The lower end of the spectrum reflects patients who received balloon dilatation only without placement of an endoscopic stent.^{6,9,27,52,89,92,95} More than 40% of patients require more than one endoscopic intervention due to stent occlusion, stent dislocation, or restenosis.^{27,52,95} The cumulative success rates after an average of two or three interventions is ~85 to 90%.^{22,52,94} Complications such as pancreatitis and cholangitis occur in ~3 to 7%.^{9,27,52,91} The risk of infection secondary to endoscopic manipulation and sphincterotomy is real in this immunosuppressed population of patients. In an effort to reduce this risk, some authors have advocated placing an internal stent above the sphincter of Oddi without performing sphincterotomy.²⁷ However, no prospective, randomized studies are available to validate this opinion. In the hands of an experienced endoscopist, the advantages of endoscopy are several and include the ease of the procedure and absence of an external "tube" for several months as well as procedural and catheter migration complications. The risks of hemorrhage, subcapsular hematoma, and peritonitis in a patient with ascites are practically nonexistent compared with those of the percutaneous approach.

The type of reconstruction determines the choice of nonsurgical intervention. Although ERCP is usually the modality of choice with distal strictures in a duct-to-duct anastomosis, endoscopic visualization is limited in a duct-to-jejunum anastomosis, necessitating percutaneous transhepatic or transjejunal interventions. Technical success rates using percutaneous techniques are high and the stricture can be crossed in more than 90% of the patients.^{1,88,96} However, as with endoscopic treatments, primary patency is achieved only in ~55%,^{7,16,88,96} and most patients require two to four dilatations to achieve long-term patency (ranging from 2 to 10 years). Following two to four dilatations, 50 to 80% of patients require no further treatment. Surgical revision is needed in 18 to 30% of patients.^{1,2,32,60,85,88,96,97} Methods to measure the success of balloon dilatation after percutaneous biliary

drainage have been described in the literature. The two common ways to determine whether a patient can be made "tube free" are manometry and a clinical trial; both appear to have similar results. Unfortunately, some patients (15–25%) develop recurrent strictures after being successfully treated,^{96,97} and most of them can be successfully retreated with nonsurgical interventions. Although many studies report a low complication rate with percutaneous interventions, complications have been well described and include bleeding, hemobilia, cholangitis, pancreatitis, pneumothorax, pleural effusion, and empyema.^{1,62,96,98} Transhepatic catheter placement across the stricture offers certain advantages. The catheter itself maintains the patency of the anastomosis while allowing repeated access to the stricture for evaluation and dilatation without any significant additional morbidity. These catheters also offer an advantage in management of strictures complicated by significant debris, as daily flushing can get rid of most debris. If that fails, the catheter can provide access for percutaneous cholangioscopy and debris or stone removal. In patients who develop cholangitis, the catheter can be opened for gravity drainage to allow external decompression of the biliary system and resolution of symptoms.

Davidson et al studied the influence of nonsurgical management of post-OLT biliary complications on the outcome of patients requiring surgical revision with Roux-en-Y choledochojejunostomy. Patients with a variety of biliary complications who initially underwent endoscopic or percutaneous interventions, failed, and then proceeded to a choledochojejunostomy were compared with patients who proceeded straight to surgery. There was no demonstrable advantage of one over the other. On the other hand, there was a trend toward a lower complication rate after choledochojejunostomy in those who underwent a failed nonsurgical approach than those proceeding straight to surgery. Some studies report a higher primary patency rate with surgery.¹⁶ However, the relatively high mortality rate with revision to a choledochojejunostomy (6%)⁹⁹ validates a nonsurgical intervention as the initial treatment, reserving surgical revision for patients in whom nonsurgical treatment fails.

The use of metallic stents across biliary strictures in the setting of transplantation has been described. In the series by Diamond et al, the cumulative primary, primary assisted, and secondary patency rates were 50, 61, and 80%, respectively, at 18 months.¹⁰⁰ In another series described by Culp et al, the primary patency rate was 44% at 3 years and 0% at 5 years with a secondary patency of 88%.¹⁰¹ Metallic stents frequently occlude and, more important, make surgical revision extremely difficult. When attempting to manipulate, remove, or divide the stent, significant tissue damage results and makes the stented portion of the duct unusable. With

Figure 3 Multiple strictures (intrahepatic and extrahepatic) are noted in this patient after liver transplantation. The etiology in this patient is not known but the differential diagnostic possibilities include CMV infection, graft-versus-host reaction, and ischemia (hepatic artery thrombosis or prolonged cold ischemia time). (Courtesy of Scott O. Trerotola, M.D., Hospital of the University of Pennsylvania.)

the current technology, there is no role for metallic stents in the management of benign biliary strictures.

Hilar and Diffuse Intrahepatic Strictures

In an extensive analysis performed by Guichelaar et al, 749 consecutive liver transplant patients were studied prospectively. Nearly 10% of these patients developed nonanastomotic strictures²⁵ (Fig. 3). Similarly, Campbell et al reported an incidence of 8.2% in their series of 1590 grafts.⁴⁰ These strictures tend to occur earlier than anastomotic strictures, often in the peri-transplantation period.⁸² They occur predominantly at the hepatic bifurcation, but often there are multiple strictures involving both the intra- and extrahepatic ducts.⁴² They have a more complex etiology and have been associated with varying factors including ischemia, pretransplantation diagnoses of PSC, HAT, and hepatic artery stenosis; choledochojejunostomy; prolonged cold ischemia time; and autoimmune hepatitis.^{8,25,32,38,40,45,68,73,94} Because of the ischemic nature, a large number of the nonanastomotic strictures occur in conjunction with biliary sludge, necrotic debris, and leaks.^{24,38,86,94} Nonanastomotic strictures can be treated nonsurgically using the same endoscopic and percutaneous techniques as those used for anastomotic strictures. However, due to the underlying etiological factors, graft dysfunction and involvement of multiple ducts are common. These strictures tend to be less responsive to nonsurgical therapy and require surgery.^{8,19,23,24,40,97} As many as 30 to 50% of these patients either die as a result of this complication or require retransplantation.^{19,24–26,32,73,86} Sanchez-Urdazpal and

Figure 4 A stone is noted in the common hepatic duct of this patient 9 years after liver transplantation. It was treated with percutaneous drainage and percutaneous lithotripsy removal under percutaneous cholangioscopic guidance (not shown). (Courtesy of Scott O. Trerotola, M.D., Hospital of the University of Pennsylvania.)

colleagues reported a 1-year graft survival of 69% as opposed to 88% in patients without these strictures.⁴⁵

Choledocholithiasis

In the early years of transplantation the discovery of debris and biliary cast material led to speculation about physiologic compositional changes in bile following transplantation.^{102,103} Compositional changes do occur after transplantation, but whether they have any clinically significant adverse effect has not been demonstrated. Calculi in post-transplantation systems are usually soft pigment debris associated with obstruction

Figure 5 Patient after liver transplantation. There are multiple strictures in the intrahepatic ducts. The amorphous appearance of some of the ducts is due to debris and casts. As there is a strong association between this appearance and hepatic artery thrombosis or hepatic artery stenosis, these should be sought.

and stasis (Fig. 4); however, cholesterol stones have been recovered. Composition analysis of the bile demonstrates cholesterol supersaturation. No correlation between degree of saturation and development of stones has been demonstrated.¹⁰⁴ Cholesterol supersaturation is worsened in the early postoperative period by external drainage of bile and loss of bile acids. Cyclosporine has been implicated for similar reasons in animal studies.¹⁰⁵ The incidence of biliary casts, stones, and sludge in the setting of transplantation is ~6 to 10%, of which casts and sludge account for more than half.⁴⁶ A strong association has been found between biliary casts or sludge (Fig. 5) and HAT or hepatic artery stenosis and they should be aggressively sought out and treated.^{38,46,76} Other risk factors include mechanical obstruction, infection, mucosal inflammation, and epithelial sloughing.

In 1995, Barton et al reported diagnostic and treatment options for biliary sludge. Although ultrasonography could detect sludge in one third of the patients, only contrast cholangiograms had acceptable sensitivity in detecting sludge.⁸⁰ Oral chemolysis was effective in only 40%, and oral chemolysis combined with percutaneous or endoscopic interventions was successful in 60% of the patients. Surgery was effective in 86%; however, it was associated with additional morbidity and mortality related to the surgery itself.¹⁰⁶ Endoscopy has not proved to be beneficial in removing casts,⁸⁷ but a percutaneous biliary drain can offer several advantages. Daily flushing of the drainage catheter helps irrigate the biliary system and wash out the debris. In addition, a transhepatic cholangioscope can be used in removing casts, debris, and stones. It can also be used to seek out the offending cause (i.e., stricture causing mechanical obstruction). Biliary casts, like nonanastomotic strictures, are often associated with underlying graft dysfunction and ischemia, and often reexploration is essential to salvage the graft.

BILIARY DILATATION WITHOUT STRICTURE AND SPHINCTER OF ODDI DYSFUNCTION

Changes in the caliber of the extrahepatic ducts without obstruction have been reported after transplantation. Campbell et al reported an average increase of 1–2 mm in the diameter of native as well as donor extrahepatic ducts without any evidence of obstruction.¹⁰⁷ Greater degrees of dilatation of the cystic duct remnant along with liver enzyme abnormality have been attributed to obstruction of the distal bile duct. Obstruction of the distal recipient bile duct may be due to pancreatitis, cholelithiasis, pancreatic mass, and hilar adenopathy. Distal biliary obstruction occurring at the papilla may be related to sphincter of Oddi dysfunction. The diagnosis is supported by improvement in liver enzymes

Table 1 Biliary Manometric Perfusion Test (BMPT)

Half-strength contrast

→ 2 mL/min × 5 min

→ 4 mL/min × 5 min

→ 6 mL/min × 5 min

→ 8 mL/min × 5 min

→ 15 mL/min × 3 min

→ 20 mL/min × 2 min

Intraductal pressure < 20 cm, H₂O is interpreted as patent

If there is a question of functional patency after treatment of a biliary stricture, a Biliary Manometric Perfusion Test (BMPT) may help. Half-strength contrast material is infused with the protocol. If the intraductal pressure is less than 20 cm H₂O, the duct is functionally patent.

during externalization of a biliary drain or T-tube. Other diagnostic tests include delayed drainage of contrast material during a cholangiogram (>15 minutes), delayed biliary emptying on scintigraphy, and biliary manometry (Table 1).¹⁰⁸ Treatment options include endoscopic sphincterotomy or the more traditional conversion to a Roux-en-Y choledochojunostomy.

EXTRINSIC COMPRESSION

Other uncommon causes of biliary pathology include extrinsic compression of the hepatic duct related to cystic duct mucocoeles, lymphoma, recurrent hepatocellular cancer, and metastases to local lymph nodes. A cystic duct mucocoele is rare and is usually related to the surgical technique in fashioning the biliary anastomoses. Percutaneous aspiration, surgical excision, and drainage of the cystic duct remnant by enteric anastomosis are the usual therapeutic options.¹⁰⁹

TECHNICAL CONSIDERATIONS: PERCUTANEOUS APPROACH

Biliary strictures that are not amenable to endoscopic therapy often require PTC with biliary drainage (the specific techniques of PTC and biliary drainage are beyond the scope of this review). If the stricture can be crossed relatively easily, an internal-external drain is placed. In situations where a high-grade stricture is present and cannot be crossed, the patient is drained externally until cholangitis and sepsis resolve. When the patient has defervesced and stabilized, an attempt to cross the stricture is repeated. Ischemic types of strictures undergo evolution after initial injury. Early on, the bile ducts are soft and collapsible. There is little resistance to cholangioplasty; however, the ducts collapse after dilatation. Over next few months, the damaged areas become fibrotic. Percutaneous transhepatic biliary drains or stents (plastic) placed across strictures act as artificial conduits for bile flow until the stricture is fibrotic and less prone to recoil. At one of our institutions, the initial

cholangioplasty is performed with a 4- or a 5-mm balloon, depending on the size of the hepatic duct. Following this, the stricture has progressive cholangioplasty every 2 weeks up to 6 or 7 mm. Prior to removal of the tube, biliary manometry is performed. The principle of biliary manometry is the same as that of a Whitaker test, where the change in the biliary ductal pressure is measured during progressive increments in the volume of continuous half-strength contrast infusion into the biliary system. A pressure increase of 20 mm Hg implies increased pressure within the biliary system related to poor emptying, and the patient "fails" the manometry test. In that situation, the manometry is performed again after an additional three cholangioplasty attempts. On the other hand, the drainage catheter is removed over a wire in the patient who "passes" the biliary manometry test, and the patient's performance is monitored by serial liver function tests. The advantage of having an internal-external drain is that the tube stents the stricture to prevent recoiling during the 2-week interval between cholangioplasties. As access to the stricture is already available, additional cholangioplasties do not carry the risks of de novo percutaneous biliary drainage and cholangioplasty.

Another technique in management of biliary strictures involves progressive increase in the size of the external-internal biliary catheter ("stenting") across the stricture. The last increase to 16 to 18 French is preceded by cholangioplasty to 6 or 7 mm. The duct heals around the large-diameter biliary catheter over the next 6 months. A clinical trial is performed by placing a tube above the stricture and "capping" it without further manipulations. If the patient is asymptomatic without rise in liver function tests after 2 weeks and the cholangiogram documents patency of the stricture, the tube is removed. The data on these techniques are sparse, and neither strategy has been proved to be significantly better than the other in a large, prospective study. Like anastomotic strictures, hilar and intrahepatic strictures can be treated percutaneously, provided that they are not diffuse or involve multiple isolated segments. However, often because of associated underlying graft dysfunction, graft survival is poor and retransplantation may be necessary. The tract formed by a percutaneous biliary drain also provides easy access to the biliary tree for stone and sludge removal. Small amounts of debris can be easily removed by gently flushing saline into the biliary ducts through the existing catheter. In patients with a large amount of sludge, debris, or biliary stones, a cholangioscope can be advanced through the same tract and be used for basket extraction or for lithotripsy.

Over the years, with improvements in surgical techniques, biliary complications have decreased. However, they remain a significant cause of morbidity and mortality. A multidisciplinary approach to these complications is essential. The interventionalist is an integral

part of this team and may have an increasing role in management of complications after liver transplantation.

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