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The Incidence, Timing, and Management of Biliary Tract Complications After Orthotopic Liver Transplantation

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Objective

This study analyzed the incidence and timing of biliary tract complications after orthotopic liver transplantation (OLTx) in 1792 consecutive patients. These results were then compared with those of previously reported series. Finally, recommendations were made on appropriate management strategies.

Summary Background Data

Technical complications after OLTx have a significant impact on patient and graft survival. One of the principle technical advances has been the standardization of techniques for biliary reconstruction. Nonetheless, biliary complications still occur. A 1983 report from the University of Pittsburgh reported biliary complications in 19% of all transplants, and an update in 1987 reported biliary complications in 13.2% of transplants.

Methods

The medical records of all patients who underwent liver transplantation and were hospitalized between January 1, 1988 and July 31, 1991 were reviewed. The case material consisted of the medical records of 217 patients treated for 245 biliary complications.

Results

Primary biliary continuity was established by either choledochocholedochostomy over a T-tube (C-C, n = 129) or a Roux-en-Y choledochojejunostomy with an internal stent (C-RY, n = 85). The overall incidence for biliary complication in this large series was 11.5%. Strictures (n = 93) and bile leak (n = 58) were the most common complications (69.6%). Most biliary complications (n = 143, 66%) occurred within the first 3 months after surgery. In general, leaks occurred early, and strictures developed later. Bile leaks were equally frequent in both C-C and C-RY (27.1% and 25.9%, respectively); strictures were more common after a C-RY type of reconstruction (36.4% and 52.9%, respectively). Twenty-one patients died, an incidence of 9.6%. Fifteen of the 21 biliary-related deaths were among patients treated for rejection before the recognition of biliary tract pathologic findings.

Conclusions

Progress has been made on improving the results of biliary reconstruction after OLTx. Nonetheless, patients continue to experience biliary complications after OLTx, and these complications cause considerable loss of grafts and life. If significant additional improvement in patient and graft survival are to be obtained, the technical performance of OLTx must continue to improve.

One of the principle technical advances of liver transplantation (OLTx) has been the standardization of techniques for biliary reconstruction. The gallbladder of the donor liver is rarely preserved, and procedures such as cholecystoduodenostomy or cholecystojejunostomy have been largely abandoned. The two most widely performed biliary reconstructions after OLTx are choledochocholedochostomy (C-C) over a T-tube or choledochojejunostomy (C-RY) over an internal stent.[1]

Nevertheless, biliary complications still occur, and they are associated with significant morbidity and mortality. A 1983 report from the University of Pittsburgh described 14 biliary tract complications occurring in 75 transplants for an incidence of 19%.[2] In this report, there were two deaths directly attributable to biliary tract complication. An update in 1987 documented biliary complications in 13.2% of the transplants.[3] Although biliary leakage and anastomotic obstruction (partial or complete) are the most common complications, other potential problems include ampullary dysfunction, mucoceles, intrahepatic biliary strictures, bile cast syndrome, bilomas, hepatic abscesses, stones, and stent-related complications.[4-8] Furthermore, it must be emphasized that primary biliary tract complications must be differentiated from those secondary to arterial insufficiency.[9]

From January 1, 1988 to July 31, 1991, we performed 1792 OLTx. We undertook a retrospective study of these patients to determine whether biliary complications are still a major cause of morbidity and mortality in patients who have undergone liver transplants.

MATERIALS AND METHODS

The medical records of all patients who had undergone liver transplants; were hospitalized in the Department of Transplant Surgery, University of Pittsburgh Medical Center, between January 1, 1988 and July 31, 1991; and were followed until July 31, 1992 were reviewed. The hospital course of all patients who had a biliary complication after OLTx was studied in detail. The case material consisted of the medical records of 217 patients treated for 245 biliary complications.

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Biliary Reconstruction

Donor hepatectomy and transplantation were performed as previously described.[10] Biliary continuity was established by either a primary duct to duct anastomosis (C-C) over a T-tube or, in cases of size discrepancy, malignancy, or primary biliary disease, a C-RY over an internal stent. In both reconstructions, a single-layer anastomosis using either 5–0 or 6–0 absorbable suture material was employed. There were three complications in patients with a Waddell–Calne biliary reconstruction.

Immunosuppression

Before January 1990, patients were immunosuppressed with cyclosporine and prednisone. Beginning in February 1990, the majority of patients were treated with FK-506 and low-dose prednisone. Acute rejection episodes were treated with either methylprednisolone or OKT3. Of the 217 patients with biliary complications, 130 patients (59.9%) were treated with cyclosporine and 87 patients (41.1%) with FK-506.

RESULTS

From January 1, 1988 to July 31, 1991, a total of 1792 liver transplants were performed: 1490 transplants in adults and 302 transplants in children. Biliary continuity was nearly equally divided between C-C and C-RY. Two hundred seventeen patients were recognized as having a biliary complication. One hundred eighty-eight of these patients were adults, and 29 were children, an incidence of 12.6% and 9.6%, respectively. Two hundred six of the patients with complications were transplanted during the period of chart review. Eleven patients with complications identified during this period in fact underwent transplantation before January 1988. Therefore, the overall incidence for biliary complications in this large series of patients was 11.5%.

One hundred twenty-nine of the patients (59%) had their initial biliary reconstruction by C-C. Eighty-five patients (39%) were initially reconstructed with a C-RY. The indications for liver transplantation in these patients are summarized in Table 1.

In 28 patients, a second biliary complication developed. This was defined as a pathologic finding either

Table 1. INDICATIONS FOR LIVER TRANSPLANTATION IN 217 PATIENTS WITH BILIARY COMPLICATIONS

ESLD	No. of Patients (%)
PNC hepatitis (B, C, A)	81 (37.3)
PNC ethanol	32 (14.7)
Primary biliary cirrhosis	25 (11.5)
Sclerosing cholangitis	20 (9.2)
Biliary atresia	19 (8.7)
HCC/cholangiocarcinoma	8 (3.7)
α_1-Antitrypsin deficiency	7 (3.2)
Budd-Chiari syndrome	6 (2.7)
Fulminant hepatic failure	6 (2.7)
Hemochromatosis	4 (1.8)
Miscellaneous	9 (4.5)

ESLD: end-stage liver disease; HCC: hepatocellular carcinoma; PNC: postnecrotic cirrhosis.

different from the initial problem or a recurrent problem that occurred more than 3 months after the treatment of the initial complication.

Time Interval

The time interval during which biliary complications developed in the 217 patients ranged from days after transplantation to more than 7 years after OLTx. Slightly more than one in three (n = 83, 38%) occurred during the perioperative period (within 30 days of surgery), and two thirds of the complications occurred within the first 3 months (n = 143, 66%, Table 2). In general, most leaks occurred in the first 4 weeks after transplantation; strictures developed later. Leaks occurring after the first month were almost invariably associated with T-tube complications (Table 3).

Type of Complications

Strictures and bile leaks were the most common biliary complication after both C-C and C-RY reconstructions. These combined were responsible for 151 of the 217 complications (69.6%, Table 4). Stricture was found in 93 patients with 81 (87%) being anastomotic in nature. In the remaining 12 patients, stricture was secondary to hepatic artery thrombosis or stenosis (n = 10, 10.7%) or recurrent cancer (n = 2, 2.2%). Bile leaks occurred in 58 patients (26.7%). One half of the leaks (29 patients) were primary anastomotic complications. The remaining leaks were secondary to hepatic artery thrombosis (n = 10, 17.2%), leaks at the T-tube exit site (n = 18, 31%), or leaks from an aberrant duct (n = 1, 1.7%).

Thirty-six patients (36 of 217, 16.6%) had a clinical obstruction that was characterized by elevated hepatic function tests and dilatation of the entire biliary tree. All 36 patients were adults with a primary C-C. All diagnostic modalities failed to show an anatomic cause for obstruction in these cases. These cases were diagnosed as primary ampullary dysfunction/biliary dyskinesia. The remaining 30 patients (13.8%) had obstructive complications resulting from stones, cystic duct mucoceles, dislodged T-tubes, and retained stents.

The range of complications was different when children were compared with adults. Strictures and obstructions comprised nearly 90% of pediatric complications but only one third of the adult complications. Leaks were responsible for another one third of adult complications (n = 55) but only 10% (3 of 29) of pediatric complications. When comparing C-C to C-RY, bile leaks were equally prevalent in both. However, stricture was more common in the C-RY group (Table 5).

Twenty-eight patients had a second biliary complication after correction of the initial problem. These complications were anastomotic strictures (n = 12), bile leaks (n = 6), and biliary obstruction caused by stents, sludge, or stones (n = 10).

Mortality Rates and Graft Loss

There were 21 biliary tract-related deaths in this group for an overall incidence of 9.6%. Biliary leaks were responsible for 15 deaths, 12 of whom had undergone a primary C-RY. Six deaths were associated with hepatic artery thrombosis. Five patients died of a complication secondary to a biliary stricture. One patient died of cholangitis associated with an impacted left duct stone. Overall, 16 of the 21 deaths occurred after primary C-RY (Table 6). Biliary complications resulted in the need for 21

Table 2. TIME INTERVAL BETWEEN OLTx AND DIAGNOSIS OF BILIARY COMPLICATIONS

Time	No. of Patients (%)
0-1 mo	83 (38.2)
1-3 mo	60 (27.6)
3-6 mo	32 (14.7)
6-12 mo	18 (8.3)
1-2 yr	7 (3.2)
2-3 yr	6 (2.8)
3-4 yr	4 (1.8)
4-5 yr	2 (0.9)
5-6 yr	3 (1.4)
6-7 yr	2 (0.9)

Table 3. COMPLICATIONS/TIME INTERVAL

	0–2 Weeks	2–4 Weeks	1–3 Months	3–6 Months	6–12 Months	>12 Months
Strictures (n = 93)	17 (32.7)	10 (32.2)	22 (36.7)	15 (36.7)	8 (44.4)	21 (87.5)
Leaks (n = 58)	26 (50)	11 (35.5)	15 (25.0)	5 (15.6)	1 (5.6)	0 (0)
Ampullary dysfunction (n = 36)	1 (1.9)	3 (9.7)	17 (28.3)	7 (21.9)	6 (33.3)	2 (8.3)
Obstruction (n = 30)	8 (15.4)	7 (22.6)	6 (10)	5 (15.6)	3 (16.7)	1 (4.2)
Total	52 (100)	31 (100)	60 (100)	32 (100)	18 (100)	24 (100)

Values are no. of patients (%).

retransplants in 19 patients (14 adults and 5 children). Seventeen patients received a second graft and two patients, a third graft. Thirteen of the retransplanted patients ultimately survived (ten adults and three children). Hepatic artery thrombosis associated with a biliary complication was the indication for retransplantation in 14 of the 19 patients.

Management of Biliary Complications

After a biliary complication was diagnosed, treatment for the most part consisted of surgical repair.

Strictures

Ninety-three patients had a biliary stricture. In 44 of 47 patients (93.6%), the C-C anastomosis was converted to a C-RY. Two patients with hepatic artery thrombosis required a second liver graft, and one with a stricture of the left duct was managed with periodical percutaneous transhepatic dilatation (PTD). In 34 of 45 patients (75.5%) with a primary C-RY, the anastomosis was surgically revised, 7 (15.5%) had PTD, 3 (6.6%) had a second graft, and 1 (2.2%) with residual hepatocellular carcinoma was not treated. All 12 of the strictures arising in patients with a second biliary complication were initially treated with PTD but, ultimately, had to be surgically revised.

Table 4. OVERALL INCIDENCE AND NATURE OF BILIARY COMPLICATIONS FOLLOWING OLTx

	Total Patients (n = 217)	Adults (n = 188)	Children (n = 29)
Strictures	93 (42.8)	76 (40.4)	17 (58.6)
Leaks	58 (26.7)	55 (29.2)	3 (10.3)
Ampullary dysfunction	36 (16.6)	36 (19.1)	0 (0)
Obstruction	30 (13.8)	21 (11.2)	9 (31.0)

Values are no. of patients (%).

Leaks

Bile leaks occurred in 58 patients. Treatment consisted of converting 15 of the C-C and 1 Waddell-Calne to C-RY. One patient received a second graft, and one died before retransplantation. There were 18 leaks from T-tube exit sites. In 11 patients, the intra-abdominal T-tube tract was closed with sutures, 5 patients were surgically drained without direct repair of the biliary tree, and 2 patients were observed. Anastomotic leaks in 12 of 22 patients with a primary C-RY were revised, 8 had a second liver graft, and 2 with metastatic ovarian cancer and Pseudomonas-caused pneumonia were not treated.

Ampullary Dysfunction

Ampullary dysfunction was diagnosed in 36 patients. In eight patients, endoscopic papillotomy was attempted but failed to normalize the patient's hepatic functions. Ultimately, all 36 were converted to C-RY.

Biliary Obstruction

There were 30 patients with various causes for their biliary obstruction. Treatment was tailored to the specific type of obstruction. Retained stents were removed percutaneously in one half of the patients and surgically in the rest. The cystic duct mucoceles was surgically excised and then converted from C-C to C-RY. Obstructing T-tubes were removed, and the patients were observed for evidence of additional biliary pathologic findings. Patients with stones, sludge, and/or bile cast syndromes were all surgically explored. Stones were removed, and the biliary anastomosis was then either converted to a C-RY or revised.

Biliary Complications Treated as Rejection

During the first post-OLTx month, 83 patients were recognized as having a biliary complication; 45.7% of this group received treatment for rejection at least once

Table 5. ANALYSIS OF BILIARY COMPLICATIONS BY PRIMARY BILIARY RECONSTRUCTION AND AGE

	CC	CRY	WC	Children (<18 yr)	Adult
Stricture (n = 93)	47 (36.4)	45 (52.9)	1 (33)	17 (58.6)	76 (40.4)
Leakage (n = 58)	35 (27.1)	22 (25.9)	1 (33)	3 (10.3)	55 (29.3)
Ampullary dysfunction (n = 36)	36 (28.0)	—	—	—	36 (19.1)
Obstruction (n = 30)	11 (8.5)	18 (21.2)	1 (33)	9 (31.0)	21 (11.2)

CC choledochocholedochostomy; CRY choledochojejunostomy Roux-en-Y; WC Waddel Calne.
Values are no. of patients (%).

before recognition of the underlying biliary pathologic condition. Fifteen of the 21 biliary tract-related deaths were among this group.

DISCUSSION

Experience has taught us the proper methods of restoring biliary continuity after OLTx. Standardization of techniques has resulted in both a decrement of biliary tract complications and an overall improvement in patient and graft survival. Nevertheless, a review of 1792 cases demonstrated that, in our institution, 11.5% of all transplanted patients have a significant biliary tract complication. Although this number represents improvement over previous reports, a significant number of patients and grafts still succumb to technical problems.[1,2] It is imperative to note that more grafts are currently lost from technical complications than from rejection.[11,12]

Biliary tract complications are, however, a fact of life, and proper diagnosis and management must be achieved to minimize their impact on the final outcome. In the immediate posttransplant period, derangements in hepatic functions can be multifactorial. Mechanical problems must, however, be distinguished from immunologic problems. It is well known that liver biopsies can be misinterpreted as showing rejection in the face of biliary tract pathologic findings. This point has to be emphasized because 15 of the 21 deaths in this series occurred after the recipient was treated initially, and probably incorrectly, for rejection before recognition of the underlying biliary tract pathologic condition.[13] In general, early evaluation of the integrity of the biliary tree is an essential step in the evaluation of elevated hepatic function tests after transplantation.

Table 6. BILIARY COMPLICATIONS RESULTING IN DEATHS

	Method of Reconstruction			
Complication	CC	CRY	WC	Overall
Stricture	2/47 (4.2)	3/45 (6.6)	0/1	5/93 (5.4)
Leaks	3/35 (8.5)	12/22 (54.5)	0/1	15/58 (25.7)
Ampullary dysfunction	0/36 (0)	—	—	0/36 (0)
Obstruction	0/11 (0)	1/18 (5.5)	0/1	1/30 (3.3)

CC choledochocholedochostomy; CRY choledochojejunostomy Roux-en-Y; WC Waddel Calne.
Values are no. of patients (%).

A review of this large population has allowed us to compare and contrast this experience with multiple previous smaller reports.[2,3,14-17] Many of the findings in this report are similar to those in the previous reports; nonetheless, some important differences did emerge. Earlier reports indicate that leaks are the leading biliary complication after OLTx.[2,3] The present data demonstrate that biliary obstruction occurs nearly threefold more often than do biliary leaks. Of 217 patients with complications in this series, 159 had obstructive complications, but only 58 had biliary leaks. Sixteen of the 21 deaths were associated with biliary leaks, and only 5 of the deaths occurred in patients with obstructive complications. It is important to note that, although the incidence of biliary leaks was nearly equal for C-C and C-RY (Table 5), most of the deaths in patients with leaks occurred in those with a primary C-RY. This is not surprising because a C-RY leak is associated with a disruption of a gastrointestinal anastomosis. Hepatic artery thrombosis or stenosis often presents as a biliary tract complication.[9] We found 17% of the leaks and 10.7% of the strictures were associated with hepatic artery abnormalities. The coexistence of arterial pathologic conditions with a biliary problem must be recognized before a surgical procedure is undertaken. A biliary reconstruction or revision with an inadequate arterial supply can be disastrous in such cases. When biliary problems coexist with arterial problems, nonsurgical intermediate steps should be considered, but the definitive solution is usually retransplantation.[3,18,19]

Another important point of discussion is the management of T-tube exit site leaks after removal of the T-tube. Typically, T-tubes are left *in situ* for 3 months. This prolonged period is, in general, necessary for an adequate tract to develop between the biliary tree and the skin. The administration of steroids appears to delay the formation of this fibrous tract significantly. If a T-tube is removed and symptoms of frank bile peritonitis develop, the options that exist consist of observation, surgical correction, or the endoscopic placement of a stent across the anastomosis. Our approach has been a surgical correction of this problem. The surgical procedure is simple. The biliary tree does not have to be visualized, and all that is necessary is to irrigate the abdomen and obtain adequate drainage. The T-tube tract, if easily identified, should be sutured near the duct. We have been satisfied with this approach and have no significant experience with endoscopic management.

Although abnormalities in hepatic function during the immediate postoperative period are multifactorial, the situation is not necessarily clearer, even years after transplantation. One point that emerges is that strictures can develop years after surgery. In fact, 11% of all biliary complications were strictures that occurred between 1 and 7 years after OLTx (Table 3).

In conclusion, progress have been made over the years in improving the results of biliary reconstruction after OLTx. Nonetheless, 11.5% of our patients continue to experience complications, and this is a disturbingly high number. As our immunologic tools have improved, a higher percentage of grafts are now being lost to either primary nonfunction or technical failure than to rejection. If significant additional improvement in patient and graft survival is to be obtained, the technical performance of this challenging operation must continue to improve.

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