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Percutaneous Treatment of Biliary Strictures After Pediatric Liver Transplantation

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Background: Biliary strictures (BS) are frequent after pediatric liver transplantation (LTx) and in spite of ongoing progress, they remain a significant cause of morbidity. In children, the majority of reconstruction is hepatico-jejunal anastomosis (HJA). The aim of this study was to analyze our experience in percutaneous transhepatic treatment of BS.

Material/Methods: Between 1998 and 2014, 589 (269 living donor) pediatric LTx were performed in our institution. We retrospectively reviewed clinical data of patients with HJA who developed BS and who underwent percutaneous transhepatic biliary drainage (PTBD).


Results: Out of 400 patients with HJA, 35 patients developed BS. There were 27 cases (77%) of anastomotic BS (ABS) and 8 cases (23%) of multilevel BS (MBS). Ninety-two PTBD sessions (2.5 per patient) were performed, with successful outcomes in 20 cases (57%). Fifteen patients, after failed PTBD, underwent surgery which was successful in 11 cases. Overall good outcomes were achieved in 31 cases (88.5%). The most common complication of PTBD was cholangitis which occurred in 5.4% of the cases. We did not find any risk factors for PTBD failure, except for treatment occurring before 2007.

Conclusions: Percutaneous treatment is effective and safe in BS and is recommended as a first-line approach. The majority of patients in our study required multiple interventions, however, the overall risk of complications was low. Surgery is essential in selected cases and always should be considered if PTBD fails.

MeSH Keywords: **Biliary Tract Diseases • Liver Transplantation • Only Child**

Abbreviations: **LTx** – liver transplantation; **BS** – biliary strictures; **ABS** – anastomotic biliary strictures; **NABS** – non-anastomotic strictures; **ITBL** – ischemia type biliary lesions; **HJA** – hepatico-jejunal anastomosis; **PTBD** – percutaneous transhepatic biliary drainage; **DDA** – duct-to-duct anastomosis; **TAC** – tacrolimus; **MMF** – mycophenolate mofetil; **MRCP** – magnetic resonance cholangiopancreatography; **MBS** – multilevel biliary stricture; **DDLtx** – deceased donor liver transplantation; **CIT** – cold ischemia time; **S** – steroids; **ALF** – acute liver failure; **LDLtx** – living donor liver transplantation; **BC** – biliary complications; **ERCP** – endoscopic retrograde cholangiopancreatography

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Background

In spite of the ongoing progress in pediatric liver transplantation (LTx) biliary strictures (BS) remain a significant cause of morbidity with the incidence varying between 3.7% and 25.3% [1,2]. Usually these patients require repeated endoscopic, percutaneous or surgical interventions and may lead to graft loss in up to 14.8% of cases [3–5]. There are anastomotic biliary strictures (ABS), non-anastomotic biliary strictures (NABS), also called ischemia type biliary lesions (ITBL) or a combination of both [6]. ABS result mainly from anatomy and surgical issues like small size or multiple bile ducts, improper technique or type of biliary reconstruction [1], whereas NABS are linked with ischemic, immunological, or infectious agents [7,8]. Anticipatory diagnostic approach is of most importance in BS because of the diversity of symptoms and the frequent sub-clinical onset [9]. In children, the most frequent indication for LTx is biliary atresia, thus the majority of reconstruction is hepatico-jejunal anastomosis (HJA). In HJA, endoscopic access to biliary anastomosis is technically difficult. Thus, the gold-standard approach is percutaneous transhepatic biliary drainage (PTBD) which has gradually replaced surgery as the first-line treatment, with successful outcome reported in 76% to 89% of cases [10]. PTBD is considered safe and effective and in most centers, surgery is only reserved for severe and/or refractory strictures. The aim of this study was to analyze our experience in percutaneous management of BS after pediatric LTx.

Material and Methods

After approval of the Ethical Board at the Children's Memorial Health Institute, we retrospectively reviewed medical records of children who underwent LTx between 1998 and 2014. Within this period, there were 589 LTx (269 from living donors), and 400 patients had HJA and 189 patients had duct-to-duct anastomosis (DDA). Only patients with HJA who developed post-transplant BS and required percutaneous treatment, were included in the study. Patients with DDA who developed strictures and underwent endoscopic treatment present a distinct group which is described separately (in press). We collected clinical data: demographics, primary diagnosis, surgical data, perioperative and long-term morbidity, history of percutaneous interventions including outcome and complications, re-transplantation and mortality. Most patients received tacrolimus (TAC) with mycophenolate mofetil (MMF) and/or steroids as primary immunosuppressive regimen. All patients were under regular follow-up visits in the outpatient clinic with ultrasound scan and Doppler examination of hepatic artery and portal vein. In cases of dilatation of bile ducts or laboratory cholestasis (increased bilirubin and/or GGTP activity) diagnostic evaluation was supplemented by liver scintigraphy (HEPIDA Sc33) and magnetic resonance cholangiopancreatography (MRCP).

In selected cases, the liver biopsy was performed to exclude other causes of graft injury, like graft rejection, drug related injury or viral infection. If bile ducts were dilated, patients were referred to percutaneous intervention.

Percutaneous transhepatic biliary drainage (PTBD)

In all patients, PTBD sessions were performed under general anesthesia with intravenous antibiotic prophylaxis (a second or third generation of cephalosporin). Punctures into the liver were made through the lateral approach into the right lobe in procedures performed for whole-liver graft patients or punctures were made subxiphoid in patients with left lateral segment graft. All procedures were performed under either fluoroscopic control or ultrasound guidance. The strictures were crossed with the guidewire, and then dilated with a standard angioplasty balloon. After successful dilatation, a pigtail catheter ranging in size between a 6- and 10-French catheter (Flexima®, Boston Scientific, Ultrathane®, Cook Medical) was inserted and left for external gravity drainage. In cases of poor drainage, the catheter was flushed with saline once or twice a day. If cannulation of BS failed, external 5-French catheter was placed in the biliary tract and the patient was qualified to surgical treatment. In 2-month (± 4 weeks) intervals, cholangiogram, re-dilatation, and catheter replacement were performed. The treatment was successful when the control cholangiogram showed no significant residual stricture and there was free passage of the contrast media through the anastomosis.

According to cholangiography, ABS was defined as a sudden decrease in diameter of the anastomotic site with subsequent dilatation of the peripheral bile ducts and the lack of effective passage of contrast. NABS was defined as a multi-focal narrowing of bile ducts proximal to the biliary anastomosis. Multilevel biliary strictures (MBS) were comprised of NABS or combination of ABS and NABS.

After completion of treatment, a successful outcome was defined as full patency of the anastomotic site with spontaneous emptying of contrast on cholangiography, continuous improvement in liver function tests (LFTs) and lack of the features of biliary obstruction in radiological studies in the 6-month follow-up. An unsuccessful procedure was defined as failed cannulation of the BS, need for surgical revision of anastomosis, ineffective drainage with persistence of cholestasis after procedure, or the need for re-transplantation due to biliary complications.

In regard to the outcome of treatment, patients were divided into a good outcome group and a bad outcome group. Demographics and clinical parameters were compared between the groups accordingly.

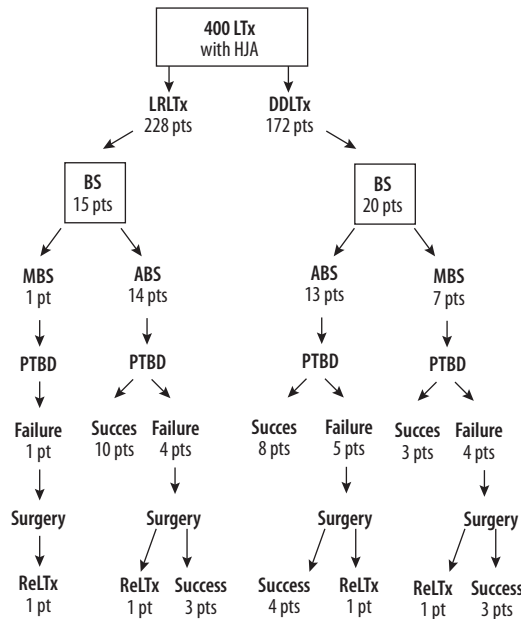


Figure 1. The outcome of percutaneous and surgical treatment in biliary strictures after LTx.

Statistical analysis

Results are presented as number, percentage, mean or median as appropriate. The differences between prognostic groups were calculated with U Mann-Whitney test and Fisher exact test for small groups. Survival rates were calculated according to the Kaplan-Meier method, with the end-point defined as re-transplantation or death, *P* value <0.05 was considered statistically significant. Statistical analysis was performed using Statistica 6.0 (College Station, Texas, USA).

Results

Out of 400 patients with HJA (228 from living donor), 35 patients developed post-transplant BS and were referred for PTBD (Figure 1). Within this group, LTx was performed at the median age of 6.7 years (range: 0.4–17.8 years). The principal indication for LTx was biliary atresia (34%) and re-transplantation (17%). Most of the BS developed within the first year after LTx (60%) and median time from LTx to the first PTBD was 0.7 years (range: 0.08–11.04 years). There were 27 (77%) ABS and 8 (23%) MBS. Patient characteristics are summarized in Table 1.

Diagnosis

In most cases, the onset was asymptomatic and the suspicion of a stricture was raised due to elevation of liver enzymes activity, bilirubin levels, and/or dilatation of bile ducts in routinely performed ultrasound scan. Clinical symptoms were present in 11 patients (31%). The most common symptoms were fever

(*n*=3), jaundice (*n*=6), itching (*n*=5), and acholic stools (*n*=2). Laboratory values at the time of diagnosis were as follows: median bilirubin 2.6 mg/dL (range: 0.5–14.8 mg/dL), GGTP 383 IU (range: 53–2996 IU) and ALT 114 IU (range: 30–282 IU). Bilirubin level was <1 mg/dL in 8 patients (23%), and GGT level below 100 IU was observed in 2 patients (6%). Ultrasound scan indicated dilatation of bile ducts in 32 patients (91%). MRCP was performed in 15 patients (43%) and all presented with dilated peripheral bile ducts. Hepatobiliary scintigraphy revealed impaired uptake in 12 patients (34%), impaired excretion in 27 patients (77%), and dilatation in 23 patients (66%). Liver biopsy was performed in 32 patients (91%). In 21 patients (66%) histopathology was consistent with biliary obstruction and presented with cholestasis and ductular proliferation.

Treatment and outcome

PTBD was successful in 20 (57%) patients and median duration of treatment was 0.4 years (0.1–3.3 years). Overall, 92 PTBD procedures were performed (mean 2.5 per patient) and most patients required more than 2 sessions of treatment (Table 2).

The most common complications after PTBD were cholangitis which occurred in 5.4% (*n*=5), perforation of duct (*n*=1), bleeding (*n*=1), and catheter displacement (*n*=2). None of these complications required surgical intervention.

Unsuccessful PTBD was mostly attributed to critical narrowing not allowing to traverse the stricture or to insufficient drainage in case of MBS. These patients were referred for surgery. Revision of HJA was performed in 14 patients with good

Table 1. Characteristics of patients presented with biliary strictures referred for percutaneous treatment.

Patient data	Number, median (range)	
Sex (Male/Female)	22/13	
Age at LTx	6.7	(0.4–17.8)
Type of LTx (DDLTX/LRDLTX)	20/15	
Type of stricture		
ABS	27	(77%)
MBS	8	(23%)
Bile leak	10	(29%)
Early stricture <1 year after LTx	21	(60%)
ABO incompatibility	3	(8%)
Donor age	34	(2.0–58)
Cold ischemia time (h)	8.25	(3.5–13.75)
Cytomegalovirus	11	(31%)
Hepatic artery thrombosis	6	(17%)
Acute rejection	20	(57%)
Indication for LTx		
Biliary atresia	12	(34.3%)
Re-transplantation	6	(17.1%)
Autoimmune hepatitis/ASC	4	(11.4%)
Hepatic tumors	4	(11.4%)
alfa1-antitrypsin deficiency	3	(8.5%)
Viral hepatitis B	2	(5.7%)
Other: Budd Chiari S. (1), PFIC1 (1), cystic fibrosis (1), ALF (1)	4	(11.4%)
Immunosuppression		
TAC+steroids	13	(37.1%)
TAC+MMF	11	(31.4%)
TAC+MMF+steroids	4	(11.4%)
Other	7	(20.0%)

outcome in 10 cases (71%). During median overall follow-up of 9.2 years (range: 1.4–18.5 years), 4 patients required re-transplantation due to progressive deterioration of graft function (Figure 1). In 3 of them, other co-morbidities of HCV infection, autoimmune hepatitis or chronic rejection, significantly contributed to graft loss. Overall, good outcome of treatment, including PTBD and surgery, was achieved in 31 patients (88.5%) and the probability of 5-year graft survival was 94%.

Table 2. The summary of PTBD treatment and outcome.

Treatment details	Number/median (range)	
Age at first PTBD years	12.4; 0.5–20.2	
PTBD good outcome	20	(57%)
Surgery before PTBD	20	(57%)
Surgery after PTBD	14	(40%)
Successful surgery after failed PTBD	10	(71%)
Overall good outcome	31	(88.5%)
Number of all PTBD (mean)	92	(2.5)
Number of PTBD		
1 session	7	(5 bad outcome)
2 sessions	9	(2 bad outcome)
3 sessions	12	(4 bad outcome)
4 and more sessions	7	(1 bad outcome)
Total duration of PTBD treatment years	0.4	(0.1–3.3)
Total follow-up after LTx years	9.2	(1.4–18.5)
Time from LTx to first intervention years	0.7	(0.08–11.04)
Follow-up after last intervention years	6.61	(0.18–12.27)

One patient was deceased after re-transplantation due non-graft related complications.

We compared several variables between groups in regard to the outcome, but only the era of treatment was significant; 80% of patients treated after 2007 had good outcome of PTBD compared to only 40% of those treated before 2007 (Table 3).

Discussion

In patients with HJA, the management of post-transplant BS is based on percutaneous and/or surgical interventions. In our experience, PTBD was effective in almost 60% of cases and another 25% of patients underwent successful surgery. Our results are similar to studies presented previously, where PTBD was effective in between 70% and 95% of cases [7,11–18]. BS are often asymptomatic, and may present with inconsistent radiological findings. Especially the dilatation of peripheral bile ducts, which is often not visualized; thus, anticipatory approach is mandatory for early diagnosis [9,14,17].

Table 3. Comparison between groups in regard to the outcome of PTBD.

	Good outcome n=20		Bad outcome n=15		p Value
Age at transplantation median (range)	5.8	(0.5–18.5)	10.7	(0.4–20.1)	0.63
Age at first PTBD median (range)	11.9	(0.8–18.7)	12.4	(0.4–24.2)	0.66
Time to PTBD median (range)	0.75	(0.5–18.5)	0.7	(0.08–4.1)	0.63
Sex					0.15
Male	11	(55%)	11	(73%)	
Female	9	(45%)	4	(27%)	
Indication for LTx					0.48
Biliary atresia	8	(40%)	4	(27%)	
Non-biliary atresia	10	(60%)	11	(73%)	
Donor type					1.00
Living	9	(45%)	6	(40%)	
Deceased	11	(55%)	9	(60%)	
Donor age median (range)	38.5	(2–58)	29	(9–54)	0.36
Recipient weight at LTx					0.71
<10 kg	5	(25%)	5	(33%)	
>10 kg	15	(75%)	10	(67%)	
Cold ischemia time (h) median (range)	7.87	(4.0–13.75)	8.75	(3.5–12.2)	0.76
Type of stricture					0.24
MBS	3	(15%)	5	(33%)	
ABS	17	(85%)	10	(66%)	
Early stricture <1y	12	(60%)	9	(60%)	0.99
Late stricture >1y	8	(40%)	6	(40%)	
Hepatic artery thrombosis – yes	3	(15%)	3	(20%)	0.99
Cytomegalovirus – yes	8	(40%)	3	(20%)	0.28
Hepatitis C virus – yes	2	(10%)	2	(13%)	0.99
ABO incompatibility – yes	2	(10%)	1	(7%)	0.99
Acute rejection – yes	12	(60%)	8	(53%)	0.74
Period of treatment					0.03
2003–2007	8	(40%)	12	(80%)	
2008–2012	12	(60%)	3	(20%)	
Surgery before PTBD – yes	9	(45%)	11	(73%)	0.16
Immunosuppression					0.27
TAC+MMF	7	(35%)	4	(27%)	
TAC+steroids	4	(20%)	9	(60%)	
TAC+MMF+steroids	4	(20%)	0	(0%)	
Other	5	(25%)	2	(13%)	
Laboratory tests before treatment mean (range)					
Total bilirubin (mg%)	3.16	(0.5–8.38)	5.08	(0.5–14.8)	0.17
GGTP (U/l)	516	(53–2996)	481	(60–850)	0.38
ALT (U/l)	108	(31–282)	131	(30–280)	0.23

In most centers, PTBD is the treatment of choice in BS, nevertheless total duration of initial approach, intervals between balloon dilatations, and timing of drain removal differ between centers, and no control trials have been performed on this topic. Usually, duration of treatment varies between 3 and 6 months with re-evaluation of the stricture every 3–4 weeks [7,11,12,14]. The mean number of PTBD courses per patient is between 2 and 4, however, a single intervention may be effective in up to 75% of cases [14,17,18].

Percutaneous treatment of BS is considered safe and effective [19], however, some proportion of patients still progress to liver cirrhosis. Feier et al. analyzed 489 pediatric after living donor LTx and 71 (14.5%) developed biliary complications. The overall mortality rate of patients with BC was 14% and the re-transplant rate was 9.8%, however, only 4.2% were directly related to BC [18]. Lorenz et al. reported an overall complication rate around 12.5%, but severe complications (sepsis and hemoperitoneum) were observed only in 2 cases (1.7%) [11]. Contraindications are rare and include uncorrectable coagulopathy, allergy to iodinated contrast, and large volume ascites [20].

Biliary strictures not responding to dilatation and stenting require surgical re-anastomosis of HJA. A combined surgical and percutaneous approach may prevent re-transplantation in the majority of patients [6,14–16,21–23]. Moreover, Darius et al., presented a surgical approach as a first-line treatment of BS with compelling results [24]. The primary patency rate of surgically treated ABS was 80% (n=47 out of 59) with a mean follow-up of 92 months (range: 1–210 months). The relapse necessitating a second surgical biliary intervention developed in 20%, however, the overall patient survival exceeded 90% regardless the type of the graft.

Data on what factors may affect the outcome of interventional treatment remains scarce and inconsistent. In previous reports, patients with hepatic artery thrombosis and NABS or combination of NABS and ABS had a higher likelihood of recurrence after percutaneous catheter removal [7,25]. Other factors, like type of the graft, history of chronic rejection, or initial diagnosis did not appear to impact the outcome [7]. Moreira et al. analyzed recipient's weight <10 kg, previous cytomegalovirus infection, donor-recipient sex and weight, autoimmune disease or biliary atresia after Kasai operation as indication for LTx, use of reduced liver grafts, and chronic or acute rejection, however, none of these variables influenced the outcome of percutaneous treatment [17].

The major goal of PTBD is to avoid unnecessary surgery, however, external long-term drainage may be very demanding for the patient and family. It might be the source of chronic discomfort and affect daily activities of the child, thus psychological support plays an important role in the adherence to treatment and overall outcomes.

The main limitation of our study was the retrospective design, the evolution of clinical approach over time, and the single-center experience. Also, the small number of patients included in the study.

Conclusions

Percutaneous methods are effective, safe, and currently recommended as the first-line treatment in post-transplant BS in patients with HJA. A close monitoring and an anticipatory approach are essential for early recognition and effective treatment. In selected patients, combination of PTBD and surgery may be required, especially in severe or refractory cases.

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