DOI: 10.15825/1995-1191-2020-3-18-25

# TREATMENT OF BILIODIGESTIVE ANASTOMOTIC STRICTURES AFTER TRANSPLANTATION OF LEFT LATERAL SEGMENT OF THE LIVER

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Many studies have shown that biliary complications after transplantation of the left lateral segment (LLS) of the liver reduce graft and recipient survival. Thus, timely correction of biliary complications, and strictures in particular, improves long-term outcomes in transplantation. **Objective:** to analyze our own experience in correcting biliary strictures in LLS graft transplantation. **Materials and methods.** From February 2014 to April 2020, 425 LLS grafts were transplanted in children. 19 (4.5%) patients were diagnosed with biliary strictures at different times after transplantation (from 0.2 to 97 months). **Results.** Biliary strictures were more often formed a year after transplantation (17.8 ± 23.9 months). In 14 out of the 19 patients, internal-external biliary drainage was successfully performed with phased replacement of the catheter with one that was larger in diameter (from 8.5 Fr to 14 Fr). The catheters were removed in 8 patients after completion of the treatment cycle. Restenosis was not observed during follow-up (13 ± 8.7 months) after the internal-external biliary drainage catheter had been removed. In 5 cases, antegrade passage of a guide wire through the stricture was unsuccessful. As a result, biliary reconstruction was performed in 4 (21.1%) patients and retransplantation was required in 1 (5.3%) patient. **Conclusion.** An antegrade minimally invasive approach can successfully eliminate biliary strictures in most children after liver LLS graft transplantation. The proposed technique is effective and safe.

*Keywords: transplantation of the left lateral segment of the liver, long-term transplant outcomes, complications, biliary strictures, correction.*

## INTRODUCTION

Transplantation of liver fragments to children dates back to the late 1980s when R. Pichlmayer was the first in the world to use the method of split transplantation of the liver dividing it along the falciform ligament into the left lateral sector (LLS) and an enlarged right lobe that included liver segments I, IV–VIII [1]. However, in 1989, Strong performed the first successful LLS transplant from a live donor, thus pioneering, with Raia [2, 3], the relative transplants. The 90s marked a breakthrough in the field of surgical hepatology and transplantology. Since the mid-90s, liver fragments transplantation has been successfully performed in many countries, including Russia, with good outcomes and chances to save previously incurable patients. However, biliary complications have remained a serious issue, *tendo Achillis* of liver transplantation [4]. At the transplantation of liver fragments, a higher rate of such complications is common. The biliary complications rate at transplantation of liver fragments in children, according to various sources, ranges from 4% to 47.4% and is about 15% in most centers [5]. Biliary complications are commonly classified as biliary fistulas, or leaks, anastomotic strictures (AS), and non-anastomotic strictures (NAS) of biliary anastomosis [6].

The main risk factors of the development of biliary complications during transplantation of liver fragments are impaired arterial blood flow, the presence of an end biliary anastomosis, and such donor-dependent factors as coagulation injury of the ducts at withdrawal, the presence of several ducts, and their small diameter [7].

To date, there are a number of minimally invasive techniques aimed at correcting biliary strictures. Endoscopic retrograde stenting can be used in children; however, because the biliodigestive reconstruction option is main in pediatric practice, this technique cannot be widely used. Such technique as the double balloon enteroscopy is used in some clinics, though it also has limitations for use in children weighing 15 kilograms or less [6].

Percutaneous techniques are actively used in children with biliodigestive anastomosis strictures in two main options, balloon dilation and external drainage. If these

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methods are ineffective, biliary reconstruction is indicated.

Of the Russian medical institutions, the Shumakov National Medical Research Center of Transplantology and Artificial Organs has the largest experience in the field of transplantation of liver fragments to children. Thus, the analysis of our own experience and a detailed presentation of the applied method of treatment of biliary strictures at the liver LLS transplantation may be both of scientific and practical interest.

## MATERIALS AND METHODS

The present study is a retrospective analysis of a prospectively populated database as well as records in medical histories, laboratory results and instrumental studies. From February 2014 to April 2020, at the Shumakov Medical Research Center, 425 LLS liver transplants were performed in children: 399 cases from relative donors, 26 cases from cadaver donors (split transplantation). In 19 (4.5%) patients, bile duct strictures were diagnosed at different times after transplantation (0.2 to 97 months). These patients have been included in the present study. The study was approved by the ethics committee of the Center.

### Immunosuppression

Immunosuppressive therapy included induction therapy with basiliximab, intravenous infusion of methylprednisolone at the time of graft reperfusion at 10 mg/kg (followed by minimization or withdrawal during the early postoperative period) and supportive therapy based on calcineurin inhibitors (tacrolimus); mycopholenic acid drugs were used optionally, in accordance with the clinical and laboratory picture. In cases of liver transplantation from blood group-incompatible related donors, the previously described preparation protocol used, which included the possibility of plasmapheresis with AB (IV) FFP replacement and rituximab administration.

### Biliary reconstruction

Biliary reconstruction was performed after vascular revascularization of the graft with the Roux limb of the jejunum. The limb was 40–50 cm long. In the case of the preceding portoenterostomy, the previously formed limb was retained under the following conditions: confidence in the limb viability (absence of extensive deserosation, multiple perforations and circulatory disorders in the limb after enterolysis), limb length over 35 cm, no history of multiple recurrent cholangitis. The anastomosis was formed with separate PDS 6.0 interrupted stitches with 1–1.5 mm duct pitch. In case of two or more ducts at less than 4 mm distance, they were combined on a preparation table or immediately before the start of biliary reconstruction along the medial walls to form a common orientation. If the unit of the ducts was impossible, separate fistulas were formed. The anastomosis was performed with 3x binocular loupes. To prevent bile leakage, the original technique of peritonization of the biliodigestive anastomosis wall with the round graft ligament was used [8]. Since September 2017, Felker external stented drainage with a 22–16 Ga catheter (depending on the ducts diameter) has been routinely used.

### Stricture diagnosis

At the transplantation center, follow-up of transplant cases is a standard practice. The protocol for inpatient and outpatient examination of children after liver transplantation includes physical examination and control of laboratory parameters as well as ultrasound of the abdominal organs. If the clinical and laboratory picture of cholestasis (including itching, GGT and bilirubin increase, stool hypocholia, etc.) or cholangitis symptoms were combined with the bile ducts expansion of more than 5 mm, the MR cholangiography was done as the basis for the biliodigestive anastomosis stricture diagnosis. At this, arterial blood flow disorders in history and characteristic MRI cholangiography and ultrasound patterns were the basis for the NAS diagnosis.

However, if the ducts dilatation was not accompanied by any clinical and laboratory changes, dynamic observation and conservative therapy, including choleretic therapy, were continued.

### Description of the technique of percutaneous transhepatic external-internal drainage

The method used for percutaneous transhepatic external-internal drainage was based, with some minor assumptions, on the technique described in detail in Feier [5]. In our practice, a Chiba 18 Ga needle was used for percutaneous puncture. The puncture was performed in the X-ray operating room (Philips Allura Xper FD 20 OR Table, Netherlands and Shimadzu Bransist alexa, Japan) under ultrasound guidance (Fig. 1). The puncture point was usually located in the epigastrium along the midline. The 2$^{nd}$ segment duct was considered optimal for drainage. After the bile intake, with the mandrel removed, a small amount of a water-soluble contrast (Ultravist 370, Optiray 350 diluted with sterile saline solution 1:4) was injected, thus partially contouring the biliary tree of the graft. After that, the guidewire was inserted, the Chiba needle was changed for II 4 Fr, 5 Fr, 6F Terumo Radifocus Introducer and with the help of various catheters (Merit Medical Performa CB1 5F, USA, Merit medical Performa KA2 4-5F, USA, Terumo Radifocus Optitorque radial TIG II 3.5 5F, Japan), diagnostic guidewires (Asahi intecc UniQual Slip-Coat Guidewire 0.035″, Biometrix Angio-Line guidewire 0.35″) and coronary guidewires (Asahi intecc Prowaterflex 0.014″, Japan; Asahi intecc Fielder 0.014″, Japan; Boston Scientific PT2 LS

0.014″ USA), we attempted to pass the stricture. In case of successful stricture passage with characteristic signs of a guidewire and contrast entering the jejunal loop (guidewire-formed "large loops", contrasting circular folds of the small intestine mucosa), a Dawson-Muller drainage (Cook Medical, USA) with 8.5 Fr diameter was installed along the guidewire with additionally formed 2–3 holes on the straight part of the drainage. If drainage was impossible due to expressed strictures, the balloon dilatation was performed (Medtronic Sprinter Legend RX balloon catheters, USA, d 1.25 mm, l 10–12 mm; d 1.5 mm, l 12–15 mm; d 2.0 mm, l 15–20 mm. The distal loop was installed in the intestine with a fixation built in the drainage (Fig. 2).

Fig. 1. Ultrasound-guided punction of the bile ducts of a liver transplant

For 2–3 days, to prevent reactive cholangitis, external bile diversion has been performed through the drainage, with the subsequent, in the absence of cholangitis signs and an improved laboratory picture, drainage block. The child was observed for several more days and discharged. Subsequently, the drainage was changed with an interval of about 3 months for large diameters (10.2; 12; 14 Fr) and upon reaching the maximum diameter, the drainage was removed with balloon control for angioplasty with a diameter of 5–7 mm (controlling the absence of a "waist" on the balloon).

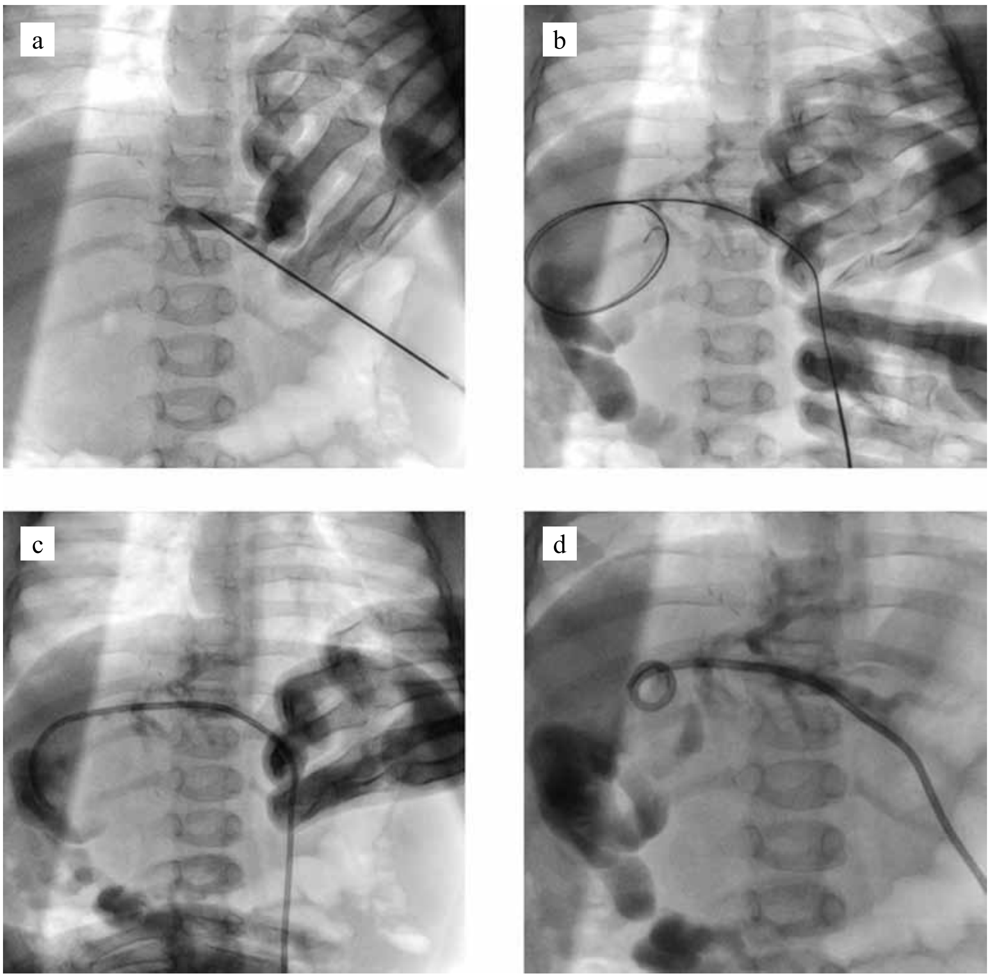


Fig. 2. The steps of an internal-external drainage set up: a – a contrast agent inserted to the dilated biliary duct; b – the guide conducted through the stricture into the Roux limb; c – the Dawson-Muller drainage passed into the Roux limb; d – the pigtale of internal-external drainage placed behind the stricture and locked

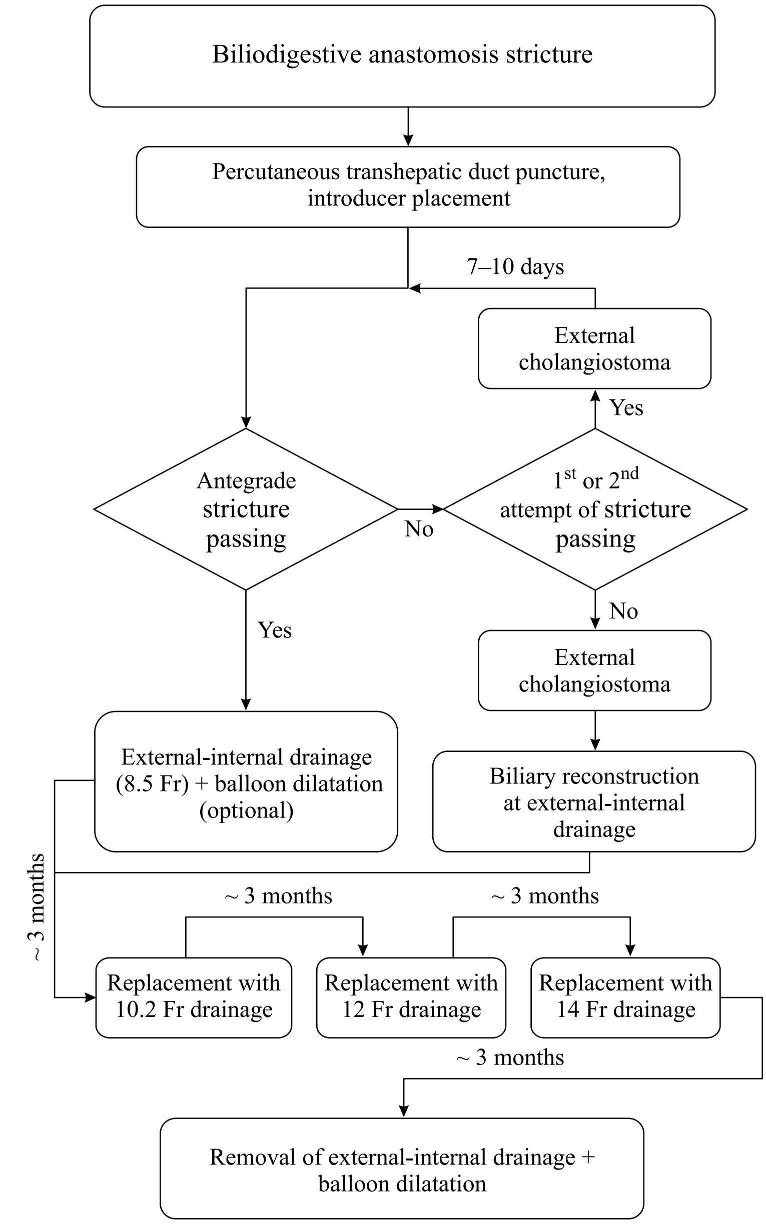


Fig. 3. The algorithm of biliary stricture management after LLS transplantation

If it was not possible to pass the stricture, an external cholangiostomy was left to decompress the bile ducts, and in 7–10 days an attempt was repeated to pass the stricture. If the stricture was not passed then, the need for the third attempt was decided individually, or biliary reconstruction was routinely performed. The algorithm is shown in Fig. 3 as a flowchart.

## RESULTS

Table 1 shows the demographic and clinical characteristics of the recipients. The most frequent disease that led to the need for transplantation in the studied patients was biliary atresia (8 cases, 42.1%) and hepatic fibrosis, or Caroli syndrome (6 cases, 31.6%). In most cases (84.2%), a related LLS transplantation was performed. More often, biliary strictures developed in over a year after transplantation (17.8 ± 23.9 months), in most cases being anastomotic (n = 17; 89.5%).

Table 2 summarizes some features of staged treatment by the above algorithm. Thus, the antegrade passage of the stricture was successful in 14 of 19 observed cases. In this, the second attempt, i. e., after the formation of an external cholangiostomy, was more often successful (n = 7; 36.8%). At the time of the article submission, in 8 out of 14 patients (42.1%), the external-internal drainage was removed, i. e., the treatment cycle was completed. Of the five cases when the antegrade stricture failed to pass, biliary reconstruction was performed in four and in one – successful liver transplantation from a cadaver donor due to the formation of secondary biliary cirrhosis.

The results of treatment in patients with antegrade external-internal stenting are given in Table 3. The time

Table 1

**Baseline demographic and clinical characteristics of LLS recipients with biliary stricture**

| Parameters | |
|---|---|
| Age*, months, mean ± SD | 27.9 ± 30.1 |
| Weight*, mean ± SD | 11.3 ± 4.3 |
| Gender, n (%) | |
| male | 11 (57.6) |
| female | 8 (42.1) |
| Diagnosis, n (%) | |
| Atresia | 8 (42.1) |
| Byler | 1 (5.3) |
| Caroli | 6 (31.6) |
| Hypoplasia | 1 (5.3) |
| Tyrosinemia | 1 (5.3) |
| Galactosemia | 1 (5.3) |
| Alpha1-Ab deficiency | 1 (5.3) |
| PELD score, mean ± SD | 21 ± 9.4 |
| Transplantation, n (%) | |
| Relative LLS | 16 (84.2) |
| Split LLS | 3 (15.8) |
| Biliary anastomoses, n (%) | |
| 1 | 13 (68.4) |
| 2 | 5 (26.3) |
| 3 | 1 (5.3) |
| Biliary stricture type, n (%) | |
| Anastomotic | 17 (89.5) |
| Non-anastomotic | 2 (10.5) |
| Stricture development after transplantation, months, mean ± SD | 17.8 ± 23.9 |

*Note.* * – at the time of transplantation; PELD – Pediatric End-stage Liver Disease.

Table 2

**Features of treatment of recipients with biliary stricture after liver transplantation**

| Parameters | |
|---|---|
| Stricture passing, n (%) | |
| At the 1st stage | 5 (26.3) |
| At the 2nd stage | 7 (36.8) |
| At the 3rd stage | 2 (10.5) |
| Failed | 5 (26.3) |
| Drainage replacement, n (%) | |
| 1 | 2 (10.5) |
| 2 | 2 (10.5) |
| 3 | 2 (10.5) |
| Full cycle (removal) | 8 (42.1) |
| Biliary reconstruction | 4 (21.1) |
| Regrafting, n (%) | 1 (5.3) |

Table 3

**The results of treatment in patients with percutaneous transhepatic antegrade external-internal drainage**

| Patients with interventional treatment (n = 14 ) | |
|---|---|
| Mean time between replacements, days, mean ± SD | |
| 1st replacement (10.5 Fr) | 101.8 ± 47.3 |
| 2nd replacement (12 Fr) | 106 ± 41 |
| 3rd replacement (14 Fr) | 110.6 ± 28 |
| Drainage removal | 115.7 ± 34.2 |
| Follow-up*, months, mean ± SD | 13 ± 8.7 |
| Outcome, n (%) | |
| Favorable | 7 (87.5) |
| Restenosis | – |
| Cholangitis episodes | 1 (12.5) |

*Note.* * – after removing the external-internal drainage.

between staged drainage replacements ranged from 101 to 116 days. The average follow-up period in 8 patients with fully completed treatment was more than a year (13 ± 8.7 months). During this period, only one of these patients developed cholangitis, which was relieved by systemic antibiotic therapy, and in no case there was a restenosis of the biliodigestive anastomosis.

## DISCUSSION

According to numerous studies, biliary complications affect the survival of both grafts and recipients [9–12].

Also, for a number of reasons, endoscopic techniques are also not always optimal. Open reconstructions often become extensive surgical interventions, especially in the long term after transplantation, due to the intensive adhesion process. An effective minimally invasive technique for correcting complications is essential for transplantology. This applies to other aspects of the liver transplant program, which makes the presence of interventional radiology an important part of the transplantation center.

The percutaneous external-internal (antegrade) drainage with stenting has gained popularity in the treatment of various kinds of strictures of the hepato-pancreato-biliary zone. The basic principles and approaches were also transposed to the treatment of biliary strictures after transplantation of liver fragments.

The present article sets out the basic principles of antegrade treatment of biliary strictures in a rather narrow category of patients, liver LLS recipients. The state of permanent drug suppression, children's age, the type of transplanted fragment and biliodigestive option of bile diversion are the distinctive features of these patients.

The use of exclusively balloon dilation without prolonged formation of an anastomosis on the frame in the form of external-internal drainage is featured by a higher rate of restenosis [13–15]. In this regard, the presented technique allows the stricture to be resolved with a good long-term effect. Also, two cases of successful treatment of such a formidable and severe complication as NAS should be noted, which made it possible to avoid the need for regrafting these patients. In the present study, antegrade passage of the stricture was unsuccessful in five cases, of which in four cases (21.1%) biliary reconstruction was required and in one case (5.3%) retransplantation. It should be noted that the presence of a cholangiostomy before the operation not only allowed stabilizing the patient by resolving jaundice and / or cholangitis, but also served as a convenient guide for navigation in conditions of a pronounced adhesive process. It was also made possible to comfortably form an anastomosis on the external-internal drainage.

The study was limited by a relatively small number of observations associated with the relatively low frequency of this complication (4.5%). Despite the fact that the study is single-center and non-randomized, the clinic's successful long-term experience may be useful for other medical institutions dealing with liver fragment transplantation.

## CONCLUSION

Timely diagnosis and correction of biliary strictures after transplantation of liver fragments allows avoiding the graft loss. The minimally invasive approaches with interventional radiology can effectively eliminate biliary strictures in most children after transplantation of the left lateral sector of the liver. The proposed technique is effective and safe.

*The authors declare no conflict of interest.*

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*The article was submitted to the journal on 17.06.2020*