

## **PEDIATRIC LIVER TRANSPLANTATION: INDICATIONS AND TECHNICAL PROCEDURES**

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**Abstract.** *Liver transplantation is considered a life-saving procedure, being accepted as therapeutical method in the end-stage liver diseases. For children, liver transplantation is sometimes the only one therapeutical approach, but associated with risks.*

*This study was conducted on a group of 31 children with liver transplantation for end-stage liver diseases between 2000-2009 in the Center of General Surgery and Liver Transplantation from Fundeni Clinical Institute, with the analysis of the indication for transplantation, surgical technical procedure and the postoperative outcome.*

**Keywords:** indications, technical procedures, pediatric liver transplantation.

### **1. Introduction**

In the today's surgery, liver transplantation is considered a life-saving procedure, being currently accepted as therapeutical method in end-stage liver diseases.

For both surgeons and researchers, the success of liver transplantation has led to extension of indications and at the same time to the reassessment of surgical treatment in the advanced stages of acute or chronic liver diseases, regarded without therapeutical approach.

Unlike the adult, to whom liver transplantation is considered in the terminal stage of liver disease, for children this can be sometimes the only one therapeutical option associated with important risks.

The first pediatric liver transplantation was performed by Professor T. E. Starzl in Denver, Colorado in 1967, to a one-year patient with hepatolastoma, with a 12-month survival. This famous achievement led to

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build up of worldwide medical centers for pediatric liver transplantation, including Romania, this approach being promising.

The major issue of transplantation is the shortage of donors and the continuous increase of patients on the waiting list.

One solution would be the surgical techniques such as split, reduced-size or living-related liver transplantation which can be performed in children for whom there is a high availability of living donors.

The aim of this study is to analyze the experience of cases of pediatric liver transplantation in Romania, with the emphasis of indication, technical procedure, morbidity and ethical issues which led to final decision for performing the liver transplantation.

The first 31 pediatric liver transplantations, with successful or difficult postoperative course have tremendous importances, opening a new page in the Romanian contemporary medicine, especially transplantation surgery.

## 2. Material and method

Between 2000 - 2009, 31 pediatric liver transplantations were performed in Center of General Surgery and Liver Transplantation of Fundeni Clinical Institute.

The age of patients was between 11 months and 17 years.

**The indications** were represented by chronic liver diseases in their terminal stage - liver cirrhosis - complicated by portal hypertension, liver failure, jaundice, upper gastrointestinal bleeding, refractory ascites, spontaneous bacterial peritonitis and, in one case, liver coma.

These liver diseases were (**table no. 1**):

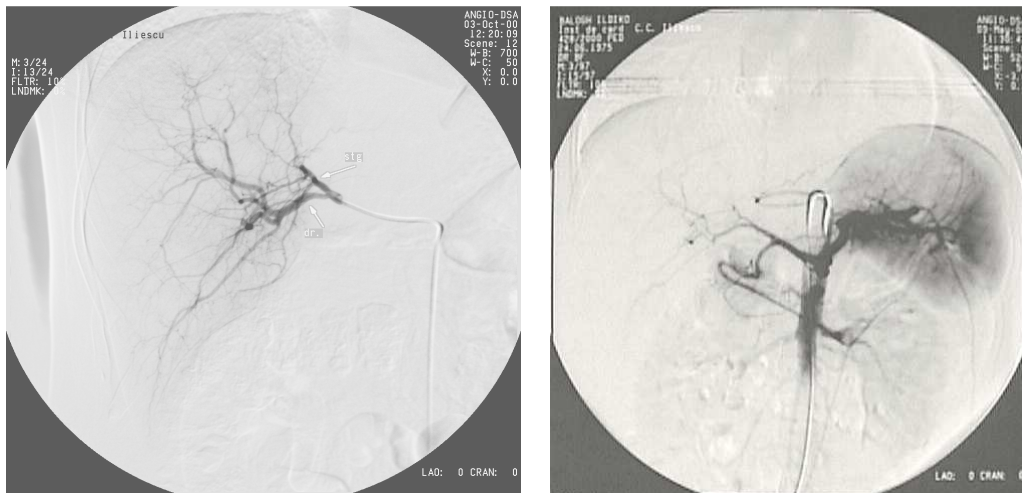
No.	Liver disease	Patient's age	Number of cases
1	Biliary atresia	11 months - 3 years	6
2	Wilson's disease	6 - 14 years	4
3	Type I glycogenosis	2 - 12 years	5
4	BHV liver cirrhosis	10 years	1
5	CHV liver cirrhosis	12 years	1
6	Autoimmune liver cirrhosis	15 years	1
7	Intrahepatic ductopenia	2 - 9 years	2
8	Hereditary fructosemia	7 years	1

9	Congenital liver fibrosis	5 - 17 years	3
10	Caroli's disease	6 years	1
11	Histiocytosis X	5 years	1
12	Focal nodular hyperplasia	15 years	1
13	Intrahepatic biliary hypoplasia	2 years	1
14	Fibrolamellar hepatocarcinoma	8 years	1
15	Primary sclerosis cholangyitis	12 years	1
16	Autoimmune hepatitis	16 years	1
Total			31

**Table no. 1:** - Indications for pediatric liver transplantations - Fundeni Center of General Surgery and Liver Transplantation

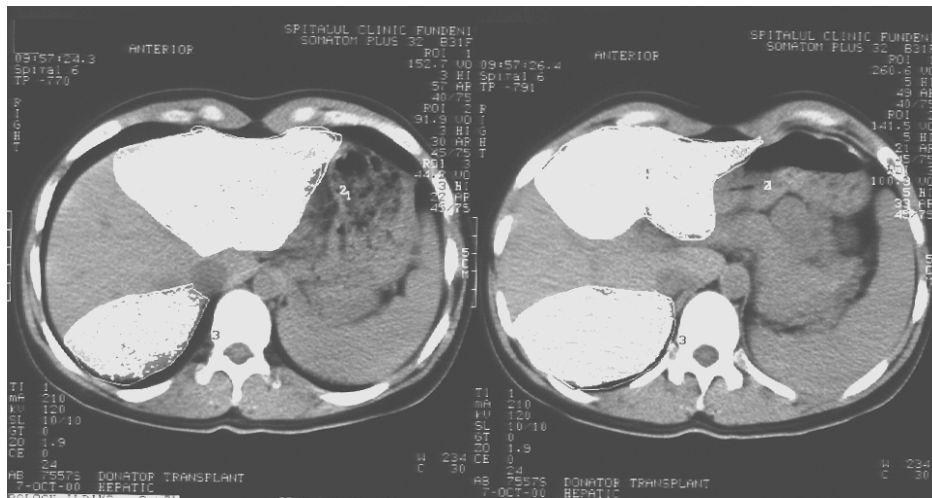
Patients were assessed preoperatively according to a standard protocol (blood, biochemical and immunologic tests, tumoral markers, radiological and endoscopic studies etc.).

In the case of living donors, great importances have selective angiography (**figure no. 1**) and computed tomography with liver volumetry (**figure no. 2**).



**A:** Arterial vascularization of donor's liver of (division of common lobe liver artery) **B:** Arterial vascularization donor's left liver

**Figure no. 1:** Selective angiography (B.I., 25-year-old).



**Figure no. 2:** CT scan. Donor's volumetry (B.I., 25-year-old).

For instance in the case of a 25 - year - old female donor, these two radiological procedures allowed the resection of liver segments II and III for a one – year - old female patient with biliary atresia.

In all cases liver transplantation was performed with the following technical variants (**table no. 2**):

No.	Patient's age	Liver transplantation variant	Number of cases
1	11 months - 11 years	living-related	25
2	12-15 years	orthotopic	4
3	5 years	split	1
4	6 years	reduced size	1

**Table no. 2.** Technical procedures for pediatric liver transplantation- Fundeni Center of General Surgery and Liver Transplantation

For the last cases liver from cadaveric donor was used, whole liver and for living-related techniques there were used liver segments II and III.

The selection of donors was made on the basis of ABO compatibility and cross-match test.

The procedure of liver transplantation occurred in three phases: donor's operation (liver procurement), back-table and recipient's operational.

**Donor's Operation** consisted of the following technical variants: liver bisegmentectomiy II - III (25 cases) for the living donors, left lobectomy (two cases) for reduced size and split technics and total hepatectomy (four cases) from cadaveric donor for orthotopic liver transplantation variant.

**II. Back-Table Procedure** has the main objective the preparation of harvested liver by removal of adipous, peritoneal and lymphatic tissue with the identification and preparation of vascular pedicles, as well as the suture of possible vascular lesions from procurement procedure or reduced size liver tissue a graft for implant to small recipient.

**III. Recipient's Operation** comprises two stages: total hepatectomy and liver implantation – reposition of the graft and suture of anastomoses in this order: caval anastomosis, portal anastomosis, hepatic artery anastomosis and biliary anastomosis. There have been made the following types of anastomoses:

- left hepatic vein (donor D) - inferior vena cava (recipient R) side-to-side or left hepatic vein (R) end-to-end;
- left branch of portal vein (D) - portal vein (R) end - to - end;
- left hepatic artery (D) - common hepatic artery (R) end - to - end;
- left hepatic duct (D) - jejunum - Roux - en - Y anastomosis; in two cases biliary anastomosis between left hepatic duct (D) and common bile duct (R).

There were 2 cases in which the arterial anastomosis was realized by the use of an arterial graft (ovarian and iliac artery from donor), because of small dimension (1 mm) of recipient's hepatic artery.

The postoperative immunosuppression regimen consisted of an inhibitory of calcineurine (tacrolimus or cyclosporine) and mycophenolate mophetil, Cel Cept; for acute rejection – Solu-Medrol or Prednol.

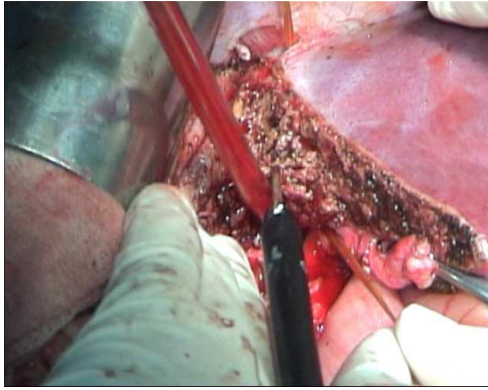
### 3. Technical Procedures

**1.** A 11 month - old female infant with a weight of 8,4 kg, diagnosed with biliary atresia and secondary cirrhosis, ventricular septal defect and 2" degree dystrophy, was admitted in our center for liver transplant, a **living related** variant being on the waiting list.

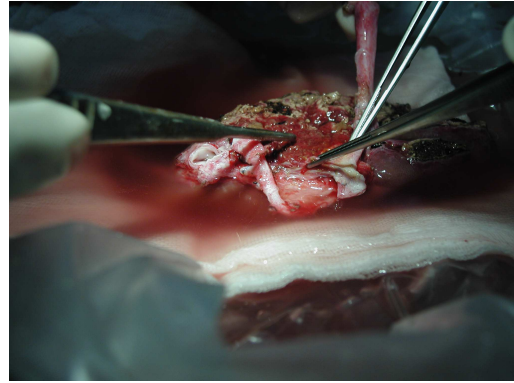
Living donor liver transplantation (mother, 25-years old), was performed in october 2000, with segments II - III, after angiography (**figure no. 1**) and CT volumetry (**figure no. 2**) assessment.

The procedure (**figure no. 3**) was divided in: donor's II-III segmentectomy (**figure 3A**), back-table (**figure 3B**) and total hepatectomy of recipient (**figure 3C**) and grafting (**figure 3D**).

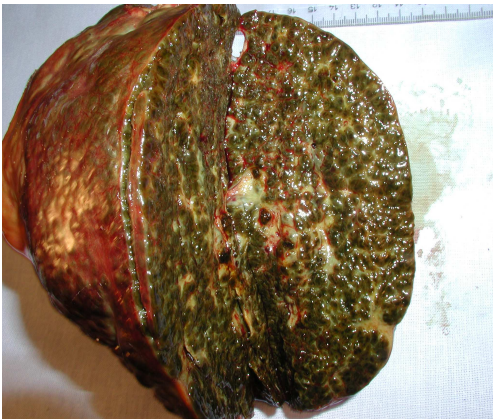
### Living Related liver transplant (A, B, C, D)



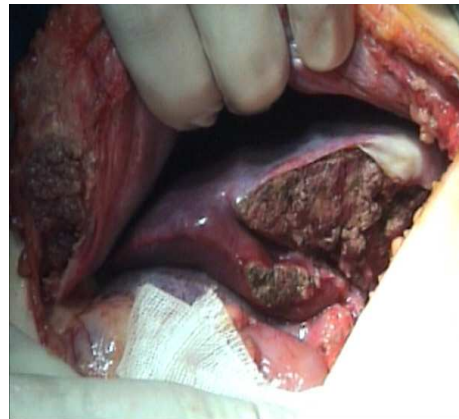
**Figure no. 3A.** Living donor's liver bisegmentectomy II-III ( 25-year-old).



**Figure no. 3B.** „Back-table”



**Figure no. 3C.** Piece of total hepatectomy a 11- month - old infant with biliary atresia and secondary cirrhosis.



**Figure no. 3D.** Liver grafting of the recipient.

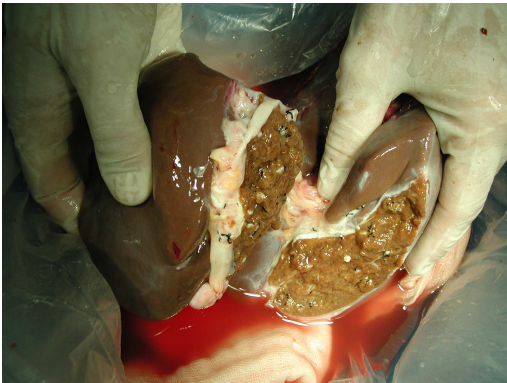
The following anastomoses were performed:

- end to end donor's left hepatic vein with recipient's left hepatic vein anastomosis,
- end to end donor's left portal branch with recipient's left portal vein anastomosis,
- end to end donor's left hepatic artery with recipient's common artery anastomosis,

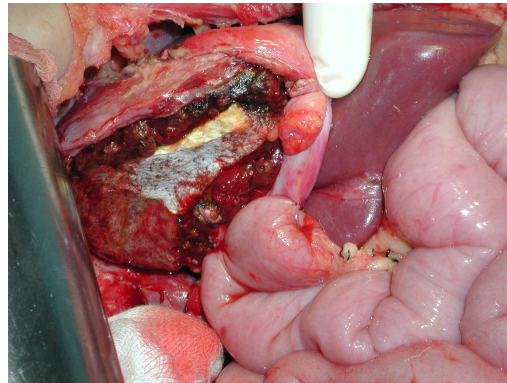
- Roux-en-Y donor's left hepatic duct with jejunal anastomosis.  
The postoperative course was good, at a present.

2. A 5-year-old female patient with type I glycogenosis with liver and muscular involvement, with recurrent severe hypoglycemia (39 mg %), found on the waiting list, was admitted in our center. **Split liver** transplantation was performed in September 2001(**figure no. 4 A, B, C**).

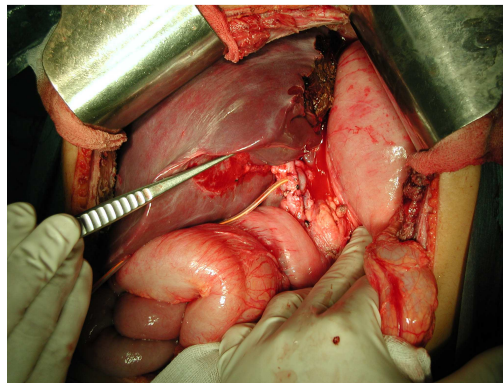
### Split liver technique



**Figure no. 4A.** Back-table procedure: ex vivo liver split in two grafts



**Figure no. 4B.** Cadaveric left liver lobe grafting to a 5-years-old patient with type I glycogen sis



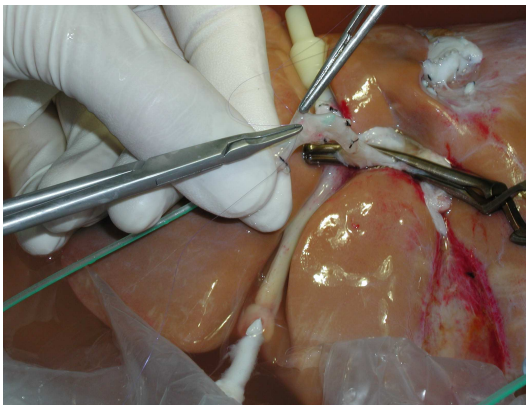
**Figure no. 4C.** Cadaveric right lobe grafting to a 21-years-old patient with familial hypercholesterolemia

The surgical technique involves the split of the cadaveric liver ex vivo in two lobes for two liver transplants: the left lobe being used for a pediatric liver transplantation and the right lobe for the adult liver transplantation.

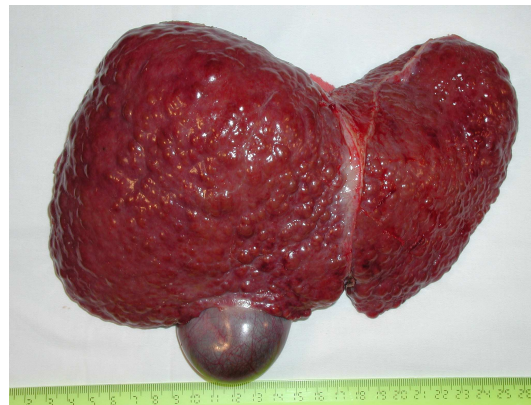


In the present case, the left liver lobe, reduced to segments II-III was used for the pediatric liver transplantation (**figure 4B**) and the right liver lobe was transplanted to a 21-years-old female patient with familial hypercholesterolemia homozygous form (**figure 4C**).

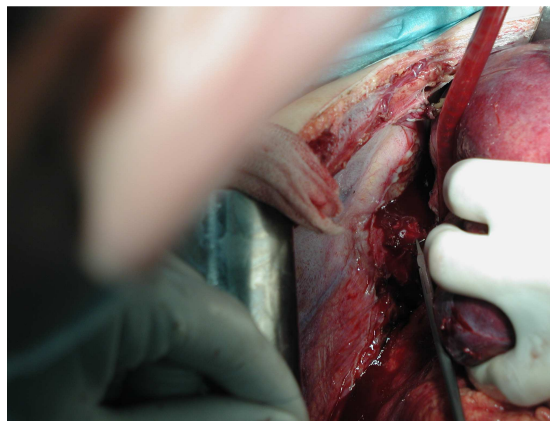
**3.** A 12-years-old male patient with Wilson's disease and Child B liver cirrhosis, splenomegaly, Kayser-Fisher corneal ring found on the waiting list, was admitted and a whole liver transplantation (**orthotopic liver transplantation**) was performed in February 2002 (**figure no. 5 A, B, C**).



**Figure no. 5A.** Back-table procedure of liver - catheterization of common liver artery.



**Figure no. 5B.** Total hepatectomy piece.: a 12-years-old patient with Wilson's disease



**Figure no. 5C.** Liver grafting (orthotopic liver transplantation)

The following anastomoses were performed:

- side-to-side donor's inferior vena cava- recipient's inferior vena cava anastomosis,
- end-to-end donor's portal vein- recipient's portal vein anastomosis,



- donor's celiac axis- recipient's common hepatic artery from superior mesenteric artery anastomosis.

- Roux en Y hepaticojejunostomy.

The postoperative course was uneventful > the immunotherapy was accomplished by Prograf and Cell Cept.

#### 4. Results

The early postoperative clinical course of patients with biliary atresia was a satisfying with a progressive decrease of jaundice and transaminases blood level, INR and improvement of serum albumin.

The same aspects were recorded in the cases of children with type I glycogenosis, Wilson's disease and liver cirrhosis complicated with coma, the latter with improvement of cerebral function after liver transplantation.

In the case of an 11- month-old child with severe malnutrition there was a significant weight gain which led to the surgical correction of ventricular septal defect with good postoperative course.

In another 7 cases, the postoperative course was unfavorable because of primary non-function of graft (one case), vascular complications (10 cases) and chronic rejection (two cases).

The postoperative morbidity of donor was insignificant.

The recipients' postoperative morbidity is predominant vascular complications (table no 4):

No.	Postoperative complications	Number of cases
1	Biliary collection	4
2	Angiocholitis	3
3	Bilio-digestive fistula	5
4	CMV, EBV, Candida infections	8
5	Pneumonia	1
6	Bronchopneumonia	1
7	Diarrhea	1
8	Hepatic artery thrombosis	9
9	Portal vein thrombosis	1
10	Late stenosis of hepatic artery	2
11	Generalized peritonitis	2

12	Intestinal obstruction	1
13	Primary non-function of graft	1
14	Acute rejection	8
15	Chronic rejection	1
16	Recurrence liver fibrosis	1

**Table no. 4:** Postoperative morbidity of pediatric recipients

## 5. Discussions

The last decade has brought a tremendous interest for pediatric liver transplantation, completely accepted as surgical treatment for end-stage liver diseases.

A classification of child's liver diseases with indications for transplantation was realized by University of Chicago [1]:

A. hereditary metabolic diseases: tyrosinemia, Wilson's disease, type I, III and IV glycogenosis,

B. viral (HBV, HCV) or autoimmune hepatitis or liver cirrhosis etc

C. intrahepatic cholestasis disease: Alagille syndrome, Byler syndrome (familial cholestasis) etc.

D. obstructive jaundice: biliary atresia, sclerosing cholangitis;

E. miscellaneous: Caroli's disease, congenital cystic fibrosis, cryptogenetic cirrhosis etc.

Thomas Starzl et col [2]. from Pittsburgh analyzing 808 cases of pediatric liver transplantations over 20 years, reported the following indications:

1. biliary atresia,

2. hereditary metabolic diseases (tyrosinemia, homozygous familial hypercholesterolemia, primary oxaluria, galactosemia, hemochromatosis, familial cholestasis, Alagille syndrome, Wilson's disease, glycogenosis),

3. viral, toxic, drug acute liver failure,

4. viral, autoimmune, cryptogenetic liver cirrhosis,

5. Miscellaneous: Budd-Chiari syndrome, hepatoblastoma, focal nodular hyperplasia nodular focal, congenital liver fibrosis, congenital cystic disease, histiocytosis X, trauma, giant hemangioma, adrenoleukodystrophy, adenoma, inflammatory pseudotumors.

The most common indication for pediatric liver transplantation is biliary atresia estimated to 62% [1] and 54,7% [2, 3]; in our group this disease was responsible of 21,7 % (6 cases).

For instance, a one-year patient, with a weight of 8.4 kg, was diagnosed with biliary atresia (**figure no. 6**), ventricular septal defect, stage II dystrophy,

secondary biliary cirrhosis, and was transplanted in 2000 - living related with segments II and III from her mother.



**Figure no. 6:** Hepatic artery thrombosis graft aspect a recipient a six years, with living related transplant for Caroli disease with secondary cirrhosis.

Thus, 90% from pediatric candidates under the age of 2 have as indication biliary atresia [1] and for this category liver transplantation is the only therapy with good outcome.

For the group 2 - 7 years, the liver diseases requiring transplantation in Fundeni Clinical Institute of Digestive Diseases and Liver Transplantation were represented by hereditary metabolic diseases based on enzyme deficiency such as: hereditary fructosemia (one case), type I glycogenosis (5 cases), as well histiocytosis X (one case), congenital liver fibrosis (one case) and Caroli's disease with liver lithiasis (one case).

Therefore, in the cases of hereditary metabolic diseases, characterized by enzyme deficiency, liver transplantation will correct this deficiency. A particular aspect is represented by homozygous familial hypercholesterolemia and glycogenosis in which the liver transplantation is associated with the regression of the disease.

For instance, a 3-year-old patient with type I glycogenosis underwent a living related liver transplantation with segments II and III with good postoperative course.

In cases of histiocytosis X, congenital liver fibrosis and Caroli's disease the liver transplantation was performed in the stage of secondary biliary cirrhosis.

Wilson's disease, focal nodular hyperplasia and autoimmune or viral liver cirrhosis have pediatric liver transplantation indications in patients of 12 - 15 years of age; in our group a particular aspect is represented by

Wilson's disease with secondary cirrhosis which was 13% of cases, different from literature 1% [1].

Due to the shortage of donors in Romania, only 1% in 2002 [4] new liver transplantation techniques developed such as living related or split for children under 10 years. One patient (12-years-old) underwent whole cadaveric liver transplantation.

It was demonstrated that the survival of patients with reduced-liver, split-liver or living related transplantation is the same with that of patient with orthotopic liver transplantation [5], and this led to the current use of these techniques. Our first pediatric living related liver transplantation was a one-year-old patient with biliary atresia who is still alive, this technique being the most common approach in our cases [6].

For all the living related liver transplantation performed in Fundeni Center of General Surgery and Liver Transplantation it was used:

- segments II and III, for 21 cases, considering the patients' age and weight,
- segments II, III and IV, for 3 cases,
- segments I,II, III and IV, for one case.

This technique has some advantages such as the lack of morbidity in donor, easy surgical procurement and good donor's acceptance.

There was no case with right lobe graft, although some authors used it in children [7, 8], with higher surgical risks, important morbidity and low acceptance.

The donor's postoperative morbidity was insignificant. It is still mentioned in literature the increased risk of pulmonary embolism, especially after right hepatectomy and coagulopathies; an example is that of a 49-year-old female patient from Belghiti J.'s series [9], who developed massive pulmonary embolism after right hepatectomy; there are also mentioned the risk of peptic ulcer, phlebitis, postoperative hemoperitoneum or biliary collections [7].

The recipient's early postoperative period was marked by viral infections (CMV and EBV), in 7 patients (70%), comparative with those from literature [1, 3, 10].

Also, there were Candida infection (one case), pneumonia (one case) and bronchopneumonia (one case).

It is important to emphasize the occurrence of these infections in the period of large immunosuppression dosages for acute rejection.

It is well known that children, unlike adults, have immature immune system and therefore are more susceptible to infections.

Paradoxically children develop rejection reactions to a greater extent (60% in our group), but are more receptive to immunosuppression.

Viral infections have greater importance, being responsible of late posttransplantation morbidity [2, 3]. Therefore, it was recorded that 22% from

all the transplanted children with EBV active infections and immunosuppression with Tacrolimus, develop lymphoproliferative disorders [1, 2, 3, 11], which in their turn, increase late mortality.

The solution of this issue would be a specific vaccine for high-risk patients or the isolation and destruction of cytotoxic lymphocytes preoperatively, both methods being currently under [5].

Also, CMV infection could play a role in the pathogenesis of chronic rejection from pediatric liver transplantation. This fact is supported by outcomes of University from Pittsburgh: double incidence of chronic rejection in CMV positive transplanted children (49%) vs. CMV negative transplanted children (26%); therefore the possibility of decrease the rate of chronic rejection is dependent on the incidence and severity of CMV infections [1, 2, 3].

In our group, a single 6-year-old child with active CMV infection, developed at 7 months after transplantation chronic rejection resistant to immunosuppression with subsequent retransplantation.

There was no lymphoproliferative disease and due to the short follow-up the longest survival is of 7 years duration

There were recorded vascular complications, especially hepatic artery thrombosis (**figure no. 6**) and portal vein thrombosis or late stenosis of arterial anastomosis.

By comparison with the adult, in pediatric liver transplantation the incidence of hepatic artery thrombosis is higher and different depending on the transplantation: 4% after whole cadaveric liver transplantation and 25% after living-related liver transplantation [12]; in the records of University from Pittsburgh, the incidence of arterial thrombosis is 19,6% (LR), with a mortality of 50% [2, 3].

The recipients with hepatic artery thrombosis was more often encountered in those cases with vascular reconstruction with arterial graft (donor's iliac or ovarian artery), with severe postoperative course and secondary acute liver failure and subsequent laparotomy for desobstruction or retransplantation.

Another risk factors would be: the child's weight below 15 kg and the age under 3 [13], the donor's large number of left accessory arteries (types II and IV of vascularisation), which is a contraindication for donation [14], arterial graft interposition, retransplantation and plasma perfusion [14], acute rejection – induces endothelial lesion with low compliance and decrease of diameter under 3 mm [12].

As consequence, one solution would be split-liver transplantation associated with a low thrombotic risk 7% [14] and whole cadaveric liver transplantation for children above 12 years: for the children under 5 months with biliary atresia a Kasai's procedure (portoenterostomy) could be an alternative to liver over a period of 6 months to one year, and subsequent transplantation [1, 13].

The hepatic artery thrombosis is a risk factor for the development of biliary complications: biliary collection, leakage, and cholangitis.

Therefore the intrahepatic biliary stenoses have been described in association with hepatic artery thrombosis or chronic rejection and probably with living-related technique [15, 16].

In our series, the association between vascular and biliary complication has been described in 10 children. Postoperative choleperitoneum, bilio-digestive fistula, anastomotic stenosis were surgically managed with good outcome. A 6-year-old child had a bilio-digestive fistula associated with chronic rejection with retransplantation at 7 months postoperatively and death.

Liver retransplantation in our series, was performed in 7 cases, with their causes: hepatic artery thrombosis (4 cases), portal vein thrombosis (one case), chronic rejection (one case), recidive of fibrosis liver disease (one case).

In this seven cases, technics variants of liver retransplantation was performed:

-reduced size: three cases,

-split liver: two cases,

-whole liver: one case,

-living related: one case.

Although associated with important morbidity and mortality, liver retransplantation is accepted as therapeutical method to increase child's life [16, 17].

The death cause was: hepatic thrombosis artery (5 cases), portal vein thrombosis (1case), hepatic thrombosis artery and portal vein thrombosis (1case), hepatic failure (2 cases), abdominal infections (2 cases), bronchopneumonia (1 case) and recurrence of hepatocarcinoma (1 case).

The lymphoproliferative disorders, hepatitis and malignant tumors, the main causes of late posttransplantation mortality [2, 3, 18, 19], were non noticed in our study group.

## **6. Ethical considerations**

There are a lot of ethical considerations which must be respected in the pediatric transplantation surgery. Due to the worldwide shortage of organs and at the same time the increase of the number of the patients on the waiting list, new liver transplantation techniques such as living donor or split procedures have been developed in order to provide a small liver graft from the living donor, usually parents.

Sometimes there is an exaggerated desire of the parents for saving their children, accepting the harvesting in any circumstances.

These issues can be solved out by a complete reassessment of the case by the transplantation team, in which the psychiatrist and psychologist's role is very important.



Upon this complete reassessment the indication can be accurately formulated, because not all the available organs are appropriate for transplantation.

There has been noticed that these surgical techniques provide a survival rate comparable with that of whole liver transplantation and are appropriate for children under the age of 5, who have less chances to receive a whole graft [9]. It is important to be stated that in children's case the graft must be of good quality although the older age of donor is not generally considered a contraindication. Some authors say that this fact is associated with high postoperative morbidity rate and recommend the usage of a graft from an aged donor in exceptional cases [16].

From ethical point of view it is not recommended to use a living donor graft to a marginal child recipient (non-resectable liver cancer) [12]. who should be include on the waiting list for a cadaveric graft.

It is also important to mention that in the process of waiting for an available cadaveric graft the chance of liver transplantation for these patients is very low.

As consequence, the transplant surgeon can face a possible dilemma: in the absence of an alternative for living donors, will leave a marginal child recipient out of the waiting list, who without a liver transplantation will die or will put the donor to a psychological morbidity out of the fact that he is witness to a palliative transplantation of a reduced-survival patient?

There are cases of long-term survival of marginal children for instance a 6-year-old patient with hepatocellular carcinoma (T4N1M0), from Pittsburgh University experience, who developed a recurrence at 4 years after transplantation [2, 3].

In all these cases, in whom the disease recurrence limits the usage of living donors graft, a possible solution could be split liver transplantation or xenotransplantation (in the case of rejection rate decrease and the control of pig viral diseases which can infect a immunosuppressant patient [6, 16].

## 7. Conclusions

Pediatric liver transplantation represents an accepted therapeutical method for end-stage liver diseases.

In our series of children, the main indications were represented by biliary atresia, type I glycogenosis, Wilson's disease and viral or autoimmune liver disease, all of them associated with liver cirrhosis

Surgical transplantation techniques such as living-related or split liver are utilized successfully in the pediatric group due to reduction of mortality on the waiting list estimated 15 - 20%.

The first 31 pediatric liver transplantations performed in Fundeni Center of General Surgery and liver Transplantation, have a great scientific, educational and historical importance due to the creation of a new pathway of pediatric liver transplantation surgery and in time new subjects of research and the development of new approaches such as: hepatocytes transplantation, xenotransplantation, gene therapy for pediatric pathology.

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