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Urgent Liver Transplantation for Biliary Atresia: The Experience in Bicêtre

FRÉDÉRIC GAUTHIER[1], CHRISTOPHE CHARDOT[1], SOPHIE BRANCHEREAU[1], YUMI OKAWA[1], OLIVIER DE DREUZY[1], DIDIER JACOLOT[2], DENIS DEVICTOR[3], DOMINIQUE DEBRAY[4] and JACQUES VALAYER[1]

[1]*Service de Chirurgie Pédiatrique,* [2]*Département d'Anesthésie-Réanimation,* [3]*Unité de Soins Intensifs pour Enfants,* [4]*Service d'Hépatologie Pédiatrique, Centre Hospitalier Universitaire Bicêtre, Faculté de Médecine Paris Sud, Université Paris 11, Le Kremlin Bicêtre, France*

GAUTHIER, F., CHARDOT, C., BRANCHEREAU, S., OKAWA, Y., de DREUZY, O., JACOLOT, D., DEVICTOR, D., DEBRAY, D. and VALAYER, T. *Urgent Liver Transplantation for Biliary Atresia: The Experience in Bicêtre.* Tohoku J. Exp. Med., 1997, **181** (1), 129-138 —— According to French rules for cadaver organ sharing, children with biliary atresia (BA) complicated with acute necrosis (ALN) can be registered on the waiting list for liver transplantation (LT) in a special intermediate grade urgent code. Over a 7 years period, 100 children have been submitted to elective LT for BA and 15 to urgent LT. Urgent procedures accounted for 25% of LT for BA in patients aged 0-2 years and 67% (8/12) in patients under 1 year of age. Children actuarial survival at 1, 12 and 48 months was respectively 66%, 60% and 60% versus 92%, 86% and 85%, deaths occuring earlier in the urgent group. Graft actuarial survival at 1, 12 and 48 months were 60%, 53% and 53% versus 85%, 77% and 76% ($p<0.05$), respectively. Outcome of children and grafts after LT is not significantly different in BA cases and in other urgent indications, excluding retransplantations. In a LT program based on cadaver organ donation, allocation of in an urgent registration code to children with BA and ALN offers them more than 50% chance to escape death and does not result in wasting of grafts. ———— biliary atresia; acute liver failure; liver transplantation

After primary or secondary failure of a Kasai operation, or in absence of Kasai operation, outcome of biliary atresia (BA) is ongoing cirrhosis. Providing adequate medical supportive care, impairment of liver function is slow and

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Address for reprints: Professeur Frédéric Gauthier, Service de Chirurgie Pédiatrique, Centre Hospitalier Universitaire Bicêtre 78, rue du Général Leclerc, F94275 Le Kremlin Bicêtre Cedex, France.

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progressive, giving time enough to bring the patient to liver transplantation (LT) in satisfactory conditions. Some of these patients waiting for LT may experience acute liver necrosis (ALN). The mechanism involved in ALN is probably an ischemic necrosis with secondary liver failure. The single chance to escape death for children suffering ALN is a prompt liver transplantation (Gartner et al. 1987; Corbally et al. 1994).

Transplantation programs in France are based mainly on cadaver organ donation, and waiting time on elective recipients list is usually several months. In the eighties, only patients with fulminant hepatic failure occuring in the absence of previous liver disease, or patients requiring an emergency retransplantation had priority and were registered on a high priority ("super urgence") list. BA patients suffering ALN during waiting period did not fulfill these conditions and had a high risk to die from ALN episode. Since 1991 it is possible, providing agreement of an expert, to register these patients on a special national urgent list of intermediate grade priority ("urgence pédiatrique"), or to shift them from elective list to this special list.

The aims of this report are: 1) to compare characteristics of patients, conditions of LT, and results in cases of urgent versus elective LT for BA, 2) to compare results of urgent LT for BA and urgent LT for other diseases in order to evaluate the validity of this rule.

Patients and Methods

Over the seven years period 1988-1995, 115 LT for BA have been performed by the pediatric surgical team of Bicêtre's Hopital. At day of LT 100 of these 115 children were registered on the elective waiting list and 15 (14%) had been registered primarily on the urgent list or had been shifted from elective to urgent list. These 15 children have been included in the study. In our experience with LT for BA, urgent LTs accounted for 25% (14/57) of LTs in patients aged less than 2 years and for 67% (8/12) of LTs performed under 1 year of age.

Following data have been collected from files of elective and urgent patients submitted to LT for BA: age at LT, donor/recipient weight ratio, intraoperative need for transfusion of blood products (including red cells concentrate and fresh frozen plasma), patient and graft survival with calculation of actuarial survival, occurence of vascular complications (hepatic artery and portal vein thrombosis) and need for reoperations. Clinical course prior to LT and pathological features of explanted liver have been reviewed in cases of urgent LT only.

Student's t-test, chi-square test and logrank test have been used as necessary to compare data between elective group and urgent group, or between BA group and the group of children submitted to urgent LT for other diseases.

TABLE 1. *Detailed data on the 15 patients*

Patient No.	Previous Kasai operation	Trigger event	Fever	ASAT peak	Prothrombin activity trough	Encephalopathy	Waiting time (days)	Age at LT (years)	Weight (kg)	Outcome and follow-up
1	Yes	Ascites paracentesis	Yes	30 N	17%	I	0	0.9	8	Dead day 0
2	Yes	None	Yes	10 N	40%	no	3	0.7	7	Dead day 1
3	Yes	None	Yes	50 N	55%	I	0	2.0	13	Alive 5.1 yrs
4	Yes	None	No	80 N	25%	no	2	1.1	9	Alive 4.2 yrs
5	Yes	None	Yes	50 N	21%	no	15	10.0	30	Alive 3.8 yrs
6	Yes	None	Hypoth.	100 N	13%	I	3	1.9	13	Dead day 48
7	Yes	Ascites	No	3 N	17%	no	0	0.6	7	Alive 3.2 yrs
8	Yes	Diarrhea (enteral nutrition)	Yes	57 N	35%	I	7	0.6	7	Dead day 1
9	Yes	Repeat G-I bleeding episodes	No	6 N	42%	II-III	15	0.6	7	Alive 1.4 yrs
10	Yes	Acute cholangitis episode	Yes	70 N	37%	no	13	1.1	10	Alive 1.3 yrs
11	Yes	Septicemia (E. Coli)	Yes	4 N	29%	I	14	1.2	9	Dead day 0
12	Yes	Diarrhea (adenovirus)	Yes	25 N	30%	II-III	8	1.3	10	Alive 0.5 yrs
13	Yes	None	Yes	5 N	17%	II-III	15	0.8	9	Alive 0.5 yrs
14	Yes	None	Yes	15 N	44%	no	1	0.9	9	Dead day 25
15	No	None	Yes	10 N	24%	II	12	0.5	7	Alive 0.4 yrs

N, upper range of normal values.
I, II, III = encephalopathy stages

Results

Clinical course

Clinical course of patients requiring urgent LT for BA is summarized on Table 1. Fourteen of the 15 patients underwent a previous Kasai procedure, with primary failure in 13 cases and secondary failure in case 5. A trigger event could be identified in 7/15 cases. Onset of ALN was marked by fever or hypothermia, rarely related to coexisting infection, in 11/15 cases. A serum ASAT peak over 10 folds maximum normal values was observed in 11/15 cases. Prothrombin activity falled under 50% of normal value in all cases except one. Mild (stage I) or moderate (stage II or III) clinical or electrical signs of encephalopathy were present in 9/15 cases. Median waiting time after registration on urgent list was 7 days (range: 0-15 days).

Pathological features

At examination of removed livers, no thrombosis of main hepatic vessels (hepatic artery or portal vein) was observed. Areas of necrosis, extending in 20% to 90% of the liver volume, were present in 11/15 livers, usually associated with large bilomas.

Conditions of LT

Median age at LT was 0.87 years (10.5 months) ranging from 6 months to 10 years. Median weight was 9 kg (range: 7-30), and weight mismatch between donor and recipient was the rule, with a median donor/recipient weight ratio of 5.6 (range: 1.2-8.6). Two children received a full-size graft, 9 a reduced size graft and 4 a partial graft, coming from a split liver in 2 cases. Average need for blood products (red blood cells and fresh frozen plasma) transfusion was 5.5 whole blood volumes (range: 1.0-17.0). Conditions of urgent LT are significantly less favorable than conditions of elective LT for BA regarding age, donor/recipient size matching and intraoperative hemorrhagic risk (Table 2).

Table 2. *Conditions of transplantation in urgent versus elective transplantations*

	Urgent LT	Elective LT	p
N	15	100	
Recipient age (years)	1.6±2.3	3.2±2.7	0.026
Donor/recipient weight ratio	5.6±2.5	3.1±2.1	<0.001
Need for transfusion (WBV)	5.5±4.4	2.7±2.5	0.001

Data are expressed as mean ± S.D.
WBV, whole blood volume.

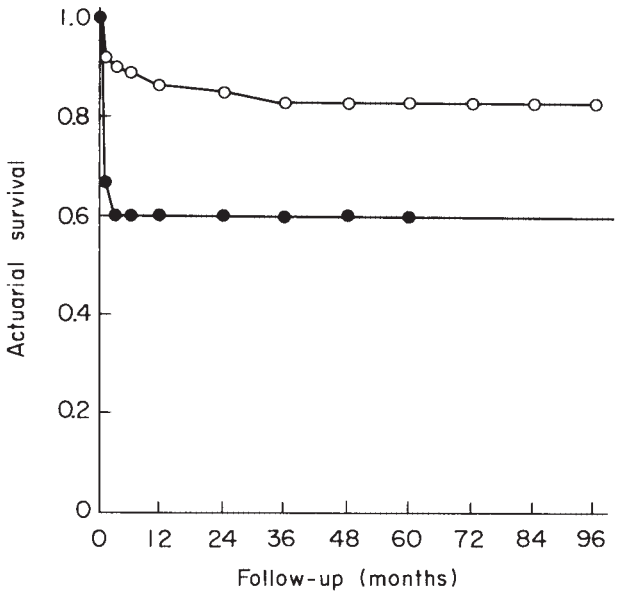

Fig. 1. Actuarial patients survival after liver transplantation for biliary atresia ○ elective liver transplantation; ● urgent liver transplantation.

Outcome

Patients survival figures

On April 30, 1996, 9 patients (67%) are alive and 6 patients (33%) and dead. Patients actuarial survival rate is 67% at 1 month, 60% at 3 months, with a plateau up to 60 months after LT (Fig. 1). Four patients died during LT or within following 24 hr, mainly from overwhelming hemorrhage, and 2 patients

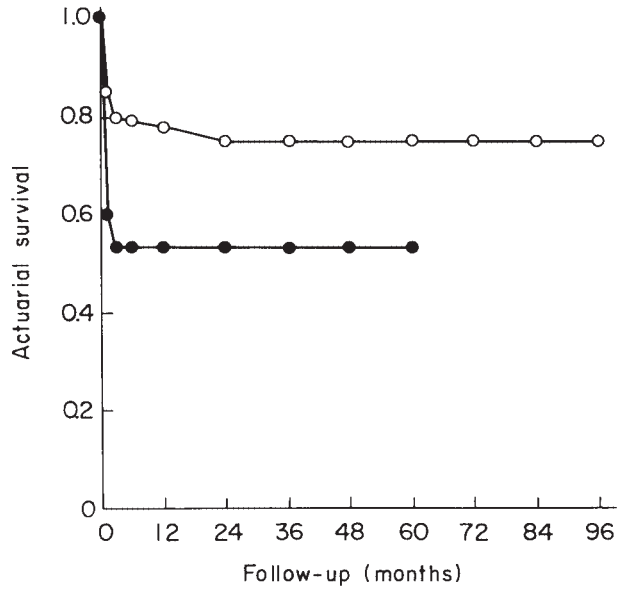

Fig. 2. Actuarial grafts survival after liver transplantation for biliary atresia See the legend of Fig. 1 for symbols.

died at 25 and 48 days respectively, from combination of sepsis and progressive multiple organ failure (Table 1). BA patients submitted to elective LT achieved a 60 months survival rate of 83%; difference between elective and urgent patients survival is significant ($p < 0.001$, Fig. 2).

Grafts survival figures

One of the survivors required a second transplantation at day 2 because of primary non-function of his first graft. Graft actuarial survival rate is then 60% at 1 month and 53% at 3 months, with a plateau up to 60 months. Graft actuarial survival rate in cases of first elective LT for BA is 75% at 60 months; difference with urgent LT is significant ($p = 0.025$).

Surgical complications

Among BA patients submitted to urgent LT, no hepatic artery thrombosis and 1 portal vein thrombosis (7%) occured. Five patients (33%) required one reoperation during their postoperative course: 2 because of persistent bleeding (1

TABLE 3. *Surgical complications in urgent versus elective transplantations*

	Urgent LT	Elective LT	Statistical analyses
n	15	100	
Hepatic artery thrombosis	0 (0%)	13(13%)	ns
Portal vein thrombosis	1 (7%)	11(11%)	ns
Need for reoperations	5(33%)	37(37%)	ns

Data are expressed as number (percentage).

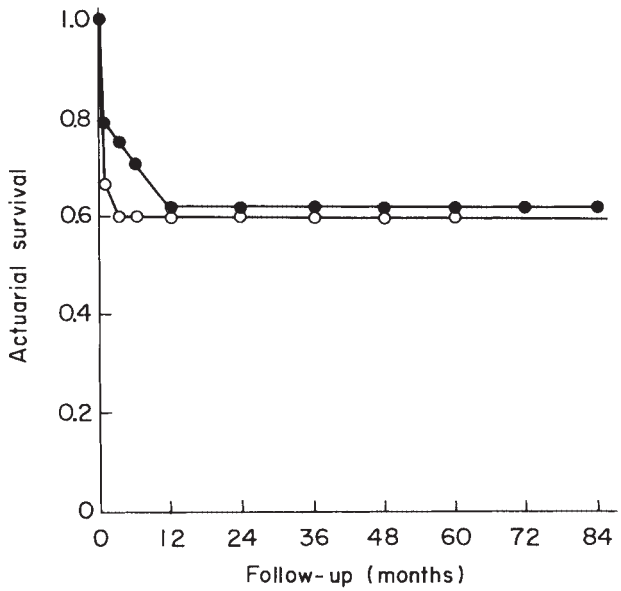

Fig. 3. Actuarial patients survival after urgent liver transplantation for biliary atresia (○) vs. other diseases (●).

is alive and 1 dead), 2 because of bowel perforation (1 is alive, and 1 dead) and 1 because of subphrenic abcess (dead). The patient with portal vein thrombosis and associated caval vein stenosis was sucessfully treated by splenorenal shunt and balloon dilatation of vena cava (Table 3).

Comparison of results of urgent LT for BA versus urgent LT for other liver disorders

Patients and grafts survival rates after urgent LT for BA have been compared

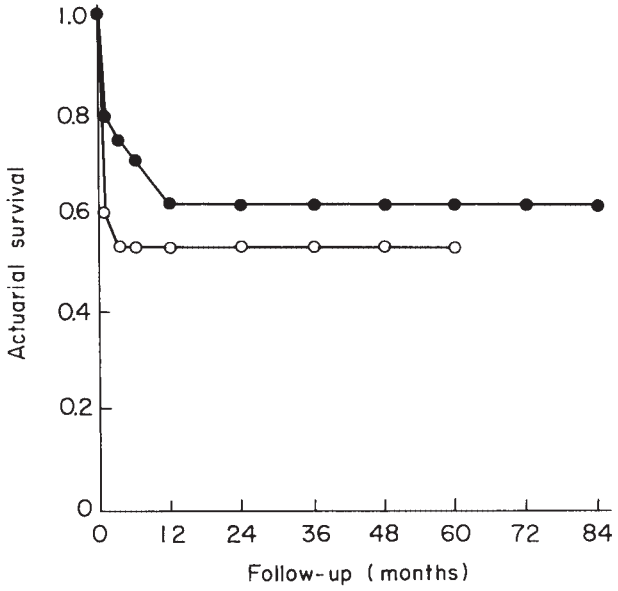

Fig. 4. Actuarial grafts survival after urgent liver transplantation for biliary atresia (○) vs. other diseases (●).

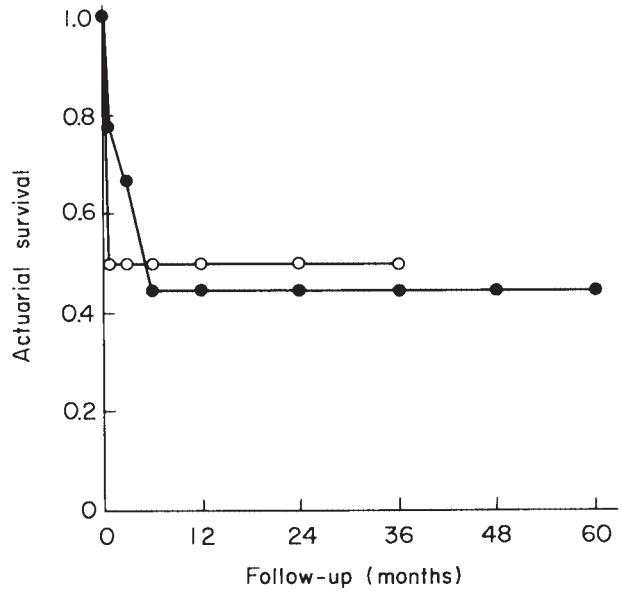

Fig. 5. Actuarial patients survival after urgent liver transplantation for biliary atresia (○) vs. other diseases (●). Patients under 1 year of age.

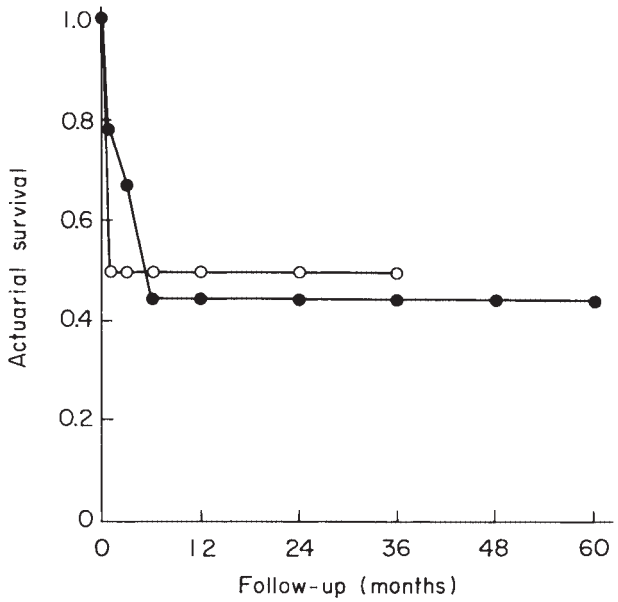

Fig. 6. Actuarial grafts survival after urgent liver transplantation for biliary atresia (○) vs. other diseases (●). Patients under 1 year of age.

to those of 24 patients requiring a first urgent LT for other liver diseases period in 24 patients. Patients 4-year actuarial survival is 60% in the BA group and 62% in the group of other patients (Fig. 3); grafts actuarial survival is 53% and 62% in both groups respectively (Fig. 4): differences are not significant. Considering only children under 1 year of age at LT (BA patients: 8; other patients: 9), patients survival figures (50% and 44% respectively; Fig. 5) and grafts survival figures (50% and 44% respectively; Fig. 6) are also not significantly different.

Discussion

Acute liver necrosis complicating BA is unfrequent. Corbally et al. (1994) reported 3 cases of ALN asessed by pathological examination, and Gartner et al. (1987) 4 cases. In the joint experience of the Bicêtre-Cochin pediatric liver transplant group, ALN occured in 10 of 196 children (5%) waiting LT for BA from 1986 to 1993. Five cases of the series presented in this paper (cases 1, 3, 5, 6, 8) are included in this group of 10 children.

The 7 patients reported by Corbally et al. (1994) and by Gartner et al. (1987) were aged 8 to 21 months at onset of ALN. All seven had undergone previous portoenterostomy. A trigger event (ascites paracentesis, gastrointestinal bleeding in two cases, or dehydratation after administration of diuretic drugs) could be identified in 4 cases. All 7 patients had encephalopathy. Five children died before LT could be performed and 2 are alive after LT. Necrosis was present in all 7 livers.

Our patient #5, had an unusual history of ALN at 10 years of age after secondary failure of a Kasai operation (KO). In case 15, ALN occured at 6 months of age, without previous KO.

Mechanisms of ALN are unclear and probably multiple. Progressive narrowing of portal vein branches in the course of BA, either after failed KO or without previous KO, has been demonstrated by Hernandez-Cano et al. (1987). It is likely that, in a liver with reduced portal blood supply, any decrease in arterial inflow, due for instance to dehydration or collapsus after severe gastro-intestinal bleeding, may induce focal or extended ischemic necrosis, and that reduction of functional parenchymal mass in a cirrhotic liver without any reserve may result rapidly in acute liver failure. A possible role of bacterial toxins has also been advocated (Mochida et al. 1990). The influence of ascites paracentesis on liver hemodynamics has been studied in adults by several authors (Kao et al. 1985; Simon et al. 1987; Gines et al. 1988). Although no case of ALN after paracentesis has been reported, all authors recommend to associate an intravenous perfusion of albumin to paracentesis in order to prevent excessive fluid loss.

Diagnosis of ALN should be suspected in any infant with BA, persistent jaundice and portal hypertension presenting with fever, abdominal pain, ascites and behaviour anomalies suggesting encephalopathy. Diagnosis of ALN is obvious when sudden and massive cytolysis, and rapid decrease in prothrombin activity are also present. It is more questionable in absence of characteristic cytolysis but must be considered if biological symptoms of liver failure arise within 24–48 hr.

Patients who could not receive a liver transplant died within ten days after onset of ALN (Gartner et al. 1987; Corbally et al. 1994). Access to urgent LT is mandatory or these children. In our experience, according to french rules for organs sharing, a graft was usually available within two weeks after registration on urgent list. These young and small size recipients are suitable for a LT performed with a partial graft and it is obvious that development of split liver transplantation programs (De Ville de Goyet 1995) will make the waiting time shorter.

Short-term results of urgent LT for BA are not so good as results of elective procedures. Nevertheless LT offers these patients about 60% chances to escape death, with a long-term survival comparable to that of elective patients.

Patients and grafts survival of children who underwent urgent LT for BA, after registration on the intermediate grade urgent list, are comparable to those of children who underwent urgent LT for other disases and who were mainly (except for children with congenital tyrosinemia presenting as acute liver failure) registered on the high priority list. Although BA patients registered on the urgent list had a chronic hepatopathy prior to acute liver failure, LTs for these patients did not result in a higher loss of grafts than LTs for patients registered on the high priority list because of fulminant hepatitis occuring on a previous normal liver. Allocation of an urgent registration code to BA patients with ALN is then widely justified.

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