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ORIGINAL ARTICLE

Paediatric acute liver failure and transplantation: The University of Essen experience

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Summary

To report our experience with 17 children who underwent a liver transplantation (LT) for acute liver failure (ALF). All LT procedures (deceased and living donor) were offered. Since 2003 Molecular Adsorbents Recycling System (MARS®) was proposed as bridging procedure. We monitored the perioperative course and the short- and long-term outcomes. All children developed pretransplant hepatic encephalopathy (mostly grades II and III); six needed ventilator support and three haemodialysis. Median PELD/MELD score was 30. MARS® was used in five children with poor pretransplant prognostic factors: all five survived the LT without sequelae. We performed 13 deceased donor LT (seven whole, five split and onr reduced) and four left lateral LDLT. Postoperative complications were observed in 10 children, requiring re-operation in seven. Two children developed irreversible neurological disorders. After a median follow up of 45 months, 16 children are still alive. About 1- and 5-year cumulative patient survival rates are 94% with a corresponding graft survival of 88% and 81%, respectively. The combination of experienced paediatric ICU management, the application of new liver support devices, and the capacity to offer both living and deceased donor transplant alternatives in a timely fashion represent the best formula to achieve optimal results in children with ALF.

Introduction

Acute liver failure (ALF) is usually defined as a syndrome characterized by an abrupt onset of jaundice and hepatic encephalopathy (HE) within 8 weeks after the development of jaundice in the absence of pre-existing liver disease [1–4]. In children, however, particularly during infancy, the manifestations of encephalopathy may be very subtle and appear very late, if ever, and ALF may be the first manifestation of an underlying metabolic problem associated with a variable degree of chronic liver damage. Perhaps a better definition of paediatric acute liver failure (PALF) is that of a multisystem disorder in which severe impairment of liver function, with or without encephalopathy, occurs in association with hepatocellular necrosis, reflected by liver synthetic failure, in a patient with no recognized underlying chronic liver disease [4–7]. Terms such as *fulminant* and *subfulminant* or *hyperacute*, *acute* and *subacute* according to the temporal onset of HE and coagulopathy have been used to further categorize ALF [6,8].

The aetiology of PALF differs according to patient age, geographical location and medical and social practices within the community (e.g. HAV in developing countries and in some areas of developed ones; HBV in endemic areas; haemophagocytic lymphohistiocytosis, cryptogenic

hepatitis and metabolic diseases which account for 75% of cases of ALF in English infants younger than 2 years) [2,3,6,9,10]. This notwithstanding, in a substantial number of cases (43–89%) the cause of ALF remains unknown [4,5,9,11,12].

Paediatric acute liver failure carries a grim prognosis with reported mortality rates ranging between 74% and 85% [3,12–17] with cerebral oedema, infection and multiple organ failure (MOF) being the main cause of death [12,18]. A spontaneous recovery occurs rarely and only 8–33% of the patients with ALF recover with medical treatment [2,3,5,6,12,13,19,20].

Liver transplantation (LT) remains the only treatment option for the majority of patients. Unfortunately only a small percentage (41–57%) of the children admitted with ALF can be transplanted within a reasonable time [2,5,12,21]. As ALF represents 5–13% of the indications for LT in paediatric patients, the cohorts of patients reported by each single centre are generally small and range between 6 and 57 cases per centre (see Table 1).

Aim

To report our experience with 17 children with ALF who underwent a LT at our centre and to compare and discuss our results based on a review of the literature.

Patients and methods

We conducted a retrospective study of all patients younger than 18 years who underwent a LT for ALF at the University Hospital of Essen from April 1998 to October 2006. *Hepatic encephalopathy* was classified in four different grades based on neurological parameters and EEG changes as follows [22–24]:

1 Grade I confusion or altered mood (EEG: minimal changes);

2 Grade II inappropriate behaviour or drowsiness (EEG: generalized slow rhythms);

3 GIII stuporous but arousable, markedly confused behaviour, hyperreflexia or positive Babinski reflex (EEG: extremely slow rhythms);

Table 1. Reports of PALF and LT in the literature.

Author/centrum	Transplants (*n*)	Technique	Patients survival	Graft survival
Pinelli [21]/Bergamo, Italy	15	10 split 4 whole 1	67 if <1 year age 83% if >1 year age	3 re-transplants
Lee [2]/Birminghan, UK	40	NR	68%	NR
Dhawan [5]/King's College, London, UK	36	NR	67%	NR
SPLIT Research Group [4]/38 LT centres from the USA and Canada	141	NR	76% (67–84%)	NR
Goss [3]/UCLA (1984–1987), Los Angeles, USA	57	38 whole 10 reduced sizes 7 LDLT 2 split	77%	65%
Rivera-Penera [12]/UCLA 1985–1993, Los Angeles, USA	38	NR	79%	NR
Devictor [25]/Bicetre, France	19	NR	68%	NR
Desphande [29]/London, UK	16	Split (*ex situ*)	93% 1 year 76.4% 3 years	89.7%
Emre [20]/New York, USA	6	LDLT	66%	50%
Liu [31]/Hong Kong	8	LDLT	62.5%	50%
Evrard and Otte [37]/Brussels, St Luc, Belgium	29	Mixed	72% at 5 years	NR
C Mack [36]/Northwestern Chicago, USA	16 with MOF	9 DDLT 7 LDLT	45% 1 month 27% 6 months 88% 1 month 63% 6 months	NR
Uemoto [34]/Kyoto, Japan	19	LDLT (16 left lat)	62%	59%
Ee [19]/Brisbane, Australia	15	NR	67% (1 month) 40% (6 months) 27% long-term	NR
Broering [38]/Hamburg, Germany	6	3 LDLT 3 split	NR	NR
Jain [39]/Pittsburgh, USA	50	NR	NR	NR

PALF, paediatric acute liver failure; LT, liver transplantation; DDLT, deceased donor LT; LDLT, living donor LT; NR, not reported; MOF, multiple organ failure.

4 Grade IVa coma without decerebrate posturing but with reaction to pain stimulus and
5 Grade IVb coma with decerebrate posturing and without reaction to pain stimulus (EEG: appearance of Delta-Waves and amplitude variations).

The *initial conservative management* of our paediatric patients consisted of:
1 causal therapy (in cases of known aetiology);
2 intense monitoring of haemodynamic, respiratory, renal, neurological, infectious, hepatic and metabolic parameters;
3 minimal handling;
4 no sedation whenever possible;
5 fluid restriction but enough fluid to assure cerebral perfusion;
6 hypercaloric protein-free nutrition;
7 intestinal sterilization with neomycine and lactulose;
8 fresh frozen plasma in case of coagulation disorder and
9 ICU in case of grade ≥II HE

Liver transplantation was *indicated* in cases of grade ≥3III HE, INR >2, bilirubin >18 mg/dl, increased tendency to hypoglycaemia, changing of liver size monitored by means of ultrasound (i.e. liver getting smaller because of necrosis).

A LT was considered *contraindicated* in cases of irreversible cerebral damage (i.e. slight cerebral oedema is not considered a contraindication), absence of uncontrolled extrahepatic infection (i.e. no SIRS), absence of uncontrolled MOF (not more than three including the liver).

Starting from 2003, Molecular Adsorbents Recycling System (MARS®, Firma Teraklin AG, Gambro/Rostock, Germany) has been used at the University Hospital Essen as a *bridging procedure* to transplant according to the following inclusion criteria:
1 INR >3 and one or more of the following:
2 HE ≥grade II;
3 creatinine values >3.5 mg/dl and oliguria (<0.5 ml/kg BW/h) and
4 hepato-renal syndrome.

With the intention to offer the best sized organ in a timely fashion, the following surgical procedures were considered for all recipients when available: deceased donor LT (DDLT; whole, reduced and split left lateral, left, right, extended right) and living donor liver transplantation (LDLT; left lateral, left, right).

All patients received an immunosuppressive induction with prednisolone prior to 2002 and since that time, with IL2R-Abs (on the day of surgery and on POD 4; $n = 5$).

Maintenance immunosuppression consisted of a dual therapy with calcineurin inhibitors (cyclosporine $n = 12$; tacrolimus $n = 5$) and prednisolone (up to 1 year post-transplant).

We monitored the intraoperative and postoperative course of each patient and noted short- and long-term outcomes.

Median values with ranges were used for numerical data. Survival curves were estimated by the Kaplan–Meier method and compared with log-rank test.

Results

From April 1998 to October 2006, our centre performed 881 LTs (143 paediatric and 738 adult in 123 and 629 patients, respectively; see Table 2). Nineteen of the 143 paediatric LT were performed in 17 children with ALF (two children were re-transplanted).

In Table 3, the demographics and the clinical presentation of ALF in the 17 patients are reported. Most of the children (15 of 17) were older than 3 years and seven were ≥12 years old.

In six cases the cause of ALF was unknown, being a form of non-A-E hepatitis in five of those six cases. All children were icteric at presentation and developed different grades of HE (mostly grades II and III). Prior to transplant, six patients needed ventilator support and three required haemodialysis. Median PELD (MELD in cases of patient age ≥12 years) was 30 (range: 7–47).

We used liver support devices as bridging procedure to LT in six cases (33%): five MARS® and one plasma separation (PS) when MARS® was not available. All five patients treated with MARS® had poor prognostic factors [HE ≥ 3 in four of them, ventilation support in four, vasopressive agents in three, brain oedema in two, median PELD score 23 (7–47)]. Median waiting time was 3 days (range: 2–5). In these five MARS®-treated patients we performed three left lateral LDLT and two full size DDLT. Patient survival and graft survival was 100% and 80%, respectively, without sequelae.

The child, who underwent PS because the MARS® system was unavailable, was an 11-year-old boy with acute Epstein–Barr viral (EBV) hepatitis. He demonstrated grade III HE with low-grade cerebral oedema, a PELD score of 25, hepato-renal syndrome, and was ventilated and needed vasopressive agents. After three sessions of PS he underwent a left lateral split LT. The graft had delayed

Table 2. Summary of the LT procedures performed at the University Hospital of Essen in the period April 1998–October 2006.

	Full size	Reduced	Split	LDLT	Total
Paediatric	46	7	53	37	143
Adult	528	1	61	148	738
Total	574	8	114	185	881

LDLT, living donor liver transplantation.

Table 3. Demographics and clinical presentation of PALF in 17 children at the University Hospital of Essen.

Age	
Mean	8.5 ± 4.9
Median	8.1 (4 months–17 years)
<3 years	2
3–11 years	8
12–18 years	7
Gender	
Male	9
Female	8
Diagnosis	
Non-A-E hepatitis	5
Wilson's disease	5
AIH	2
PCM intoxication	1
Hepatitis B	1
EBV	1
Cryptogenic	1
Budd-Chiari	1
Clinical presentation	
Hepatic encephalopathy	
Grade I	1
Grade II	6
Grade III	8
Grade IV	2
Jaundice	17/17 (100%)
Ascites	8/17 (47%)
Seizure	0/17
Ventilation support	6/17 (35%)
Pressor support	3/17 (18%)
Haemodialysis	3/17 (18%)
Laboratory values, median (range)	
INR	2.565 (1.24–8.9)
Factor V (%)	42.2 (21–76)
Bilirubin (mg/dl)	48 (1.3–69.9)
Creatinine (mg/dl)	0.56 (0.2–2.4)
NH_3 (mg/dl)	39.3 (49–396)

PELD/MELD	PELD + MELD	PELD (<12 years)	MELD (12–17 years)
Mean ± SD	29.6 ± 10	28.3 ± 9.8	31.57 ± 10.6
Median	30 (7–47)	29.5 (7–39)	30 (18–47)

Liver device	6/17 (35%)	Duration (days)
MARS	5	3 (2–4)
PS	1	2

EBV, Ebstein–Barr virus; PALF, paediatric acute liver failure; AIH, autoimmune hepatitis; MARS, Molecular Adsorbents Recycling System; PCM, paracetamol; PS, plasma separation.

primary function. He unfortunately died on POD 44 because of sepsis secondary to spontaneous intestinal perforation.

Overall, we performed 13 DDLT (seven whole, five split and one reduced size) and four left lateral LDLT for our patients with PALF after a median waiting time of 3 days (range: 1–7). The different cold and warm ischaemic times are reported in Table 4. Three patients experienced an *intraoperative* vascular complication.

Table 4. Cold and warm ischaemia times according to the transplant procedure.

	CIT (h)	WIT (min)
Total	6.3 (1.25–20.5)	34 (23–84)
Whole ($n = 7$)	6.3 (4.8–10.5)	33 (23–50)
Split ($n = 5$)	14.3 (8–20.5)	57 (30–68)
LD ($n = 4$)	2.5 (1.25–4.4)	46 (23–47)

CIT, cold ischaemia time; WIT, warm ischaemia time; LD, living donor.

1 Venous outflow congestion in a 6.5-year-old child who underwent a left lobe split LT because of non-A-E hepatitis. We performed a partial revision of the venous anastomosis and anticoagulated the child postoperatively with heparin. The anticoagulation resulted in postoperative bleeding from resection surface requiring a surgical revision. The subsequent postoperative period was uneventful. The patient is doing fine 56 months after LT.

2 Hepatic artery thrombosis (HAT) in an 11-year-old girl with acute decompensated Wilson's disease who underwent an extended right split LT. We performed a surgical thrombectomy and revision of the HA anastomosis. The postoperative course was uneventful. The patient is now in very good conditions 82 months after the operation.

3 HAT in a 4-year-old boy with ALF secondary to paracetamol intoxication who underwent a left lateral LDLT. The HA anastomosis was redone immediately, but he experienced an early recurrence of HAT on POD 1 with consequent graft loss. The child was re-transplanted 1 day later with a left lateral split LT. Sixteen months after the operation the patient is alive and doing fine.

Excluding the child with graft loss because of HAT, we observed a primary graft function in 16 of 17 LTs and delayed primary function in only one patient.

Postoperative complications were observed in 10 children (Table 5), requiring re-operation in seven and re-transplantation in one of them. Although nine of these 10 children are still alive, two of them unfortunately developed serious neurological complications/neurological disorders. One patient was an 18-month-old girl with ALF secondary to non-A-E hepatitis. She presented with grade III HE, the cerebral computerized tomographic scans showed minimal cerebral oedema and EEG was normal. Her INR was 3.5 and factor V 31%. She was ventilator-dependent but without vasopressors and without hepato-renal syndrome. The PELD score was 38. After 2 days waiting time, she underwent a left lateral LDLT. Postoperatively, although the graft demonstrated

Table 5. Postoperative complications.

Complication	*n*	Therapy	Course
Bleeding	3	Re-op	Alive
Bile leak	2	Re-op	Alive
Bile duct stenosis	1	Re-op	Alive
Neurological	2	–	Alive
Abscess	1	Re-op	Alive
HAT	1	Re-LT	Alive
HA stenosis	1	Re-op	Alive
Intestinal perforation	1	Re-op	Dead (late sepsis)

Re-op, re-operation; Re-LT, re-liver transplanatation; HAT, hepatic artery thrombosis.

perfect primary function, the child did not wake up and developed recurrent convulsions, remaining comatose with the appearance of Delta-Waves on EEG. A Cranial Computerized Tomography (CCT) scan at POD 4 revealed a generalized cerebral oedema secondary to bilateral ischaemic lesions of the posterior cerebral arteries. After 23 days in the ICU, she was admitted to the peripheral ward. Her neurological status improved slightly and was finally characterized by consciousness fluctuating between silent and agitated phases with no reaction to pain, touch or sound. Eleven months after the operation the child was alive but unfortunately in the same compromised neurological state.

The second patient was a 4-month-old boy from Kosovo, with ALF secondary to acute hepatitis B. Preoperatively, he presented with grade III HE with convulsions (CCT-negative), INR 2.3, factor V 35%, a PELD score of 29, but without hepato-renal syndrome and no need for mechanical ventilation or vasopressors. After 4 days waiting time, he received a left lateral split LT. On POD 2, he underwent re-operation because of major bleeding from the resection surface. The liver graft had a good primary function. From the neurological point of view, he had an uneventful primary course, but required neuroleptic medication for the convulsions at initial presentation. Two months after discharge he was re-admitted with deterioration in his clinical condition and with convulsions secondary to medication mismanagement by his parents. Despite re-institution of neuroleptic therapy and additional parent education, the child developed irreversible neurological deficits (i.e. muscular hypotonia, absent fine motor coordination and minimal awareness). Twenty-three months after the LT, the child was still alive but remained in a diminished mental state.

After a median follow up of 45 months (range: 16–91), 16 of 17 children are still alive. About 1- and 5-year cumulative patient survival rates are both 94% with a corresponding graft survival of 88% and 81%, respectively (see Fig. 1).

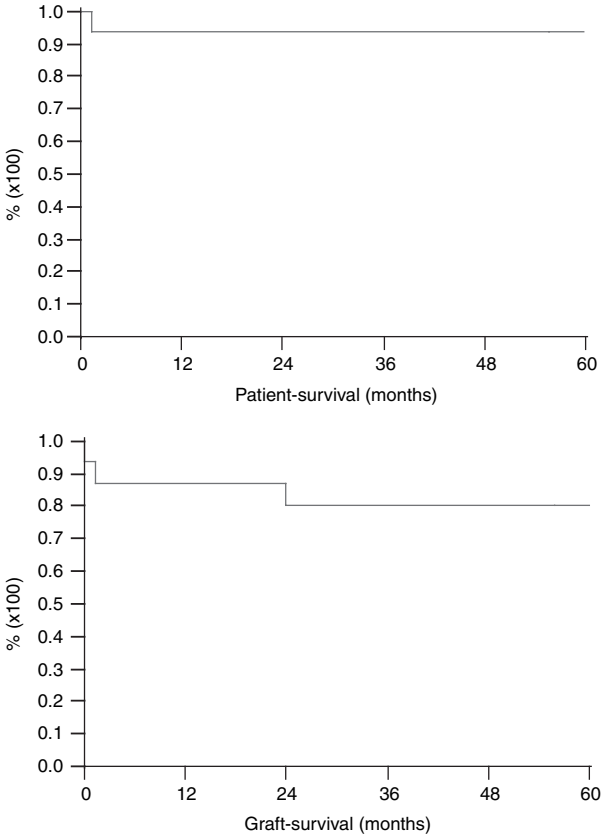

Figure 1 Patient and graft survival curves.

As reported above, an 11-year-old boy died on POD 44 from sepsis secondary to spontaneous intestinal perforation following a left lateral split LT for acute EBV-hepatitis.

In addition to the previously mentioned case of graft loss because of HAT, one other child experienced graft loss 2 years after LT. He was a 13-year-old boy transplanted for ALF secondary to autoimmune hepatitis (AIH) who developed a liver fibrosis of unknown origin 1 year after whole liver LT. Because of persistent and increasing cholestasis, he was re-listed and re-transplanted with another whole liver 2 years after the first LT. Seven months after his second LT, he is doing well.

Discussion

Liver transplantation remains the only available life-saving procedure for PALF [2,12]. Not all children with ALF, however, are suitable candidates for LT. Pretransplant neurological status, severe sepsis, MOF (especially as a result of mitochondrial cytopathy) and infiltrative diseases may all be contraindications to LT [2]. Ultimately, only

about half of children with ALF are deemed to be candidates for transplantation [2,5,12,25].

Like those patients who die before LT, mortality *after* LT is usually secondary to neurological complications, MOF and infections [4,12]. Based on multivariate analyses, the most relevant preoperative prognostic factors negatively influencing the post-transplant outcome with PALF have been reported to be the recipient age (i.e. <3 years), an INR >2.5, haemodialysis or haemofiltration, ventilator dependence and grade of HE >3 [1–5,8]. There are diverging opinions about the role of PELD/MELD score as a prognostic factor for the postoperative outcome in such cases [1,16].

The results following LT for PALF are substantially worse than those of LT for elective indications. In fact, patient survival rates are approximately 60–70% in most series (see Table 1). Unfortunately, the reported results in the literature are quite inhomogeneous, reflecting different transplant eras, centre experiences (generally with few children per transplant group), LT techniques/procedures, and clinical conditions of the patients prior to undergoing LT (Table 1). Interestingly, and for unclear reasons, very few centres report data regarding graft survival rates. While accurate comparison of the clinical presentation of patients across various reports is not always possible, we can say, based on the available data, that the clinical conditions of our patients appear to be similar to those reported elsewhere in the literature. The majority of our patients demonstrated one or more of the above-mentioned negative prognostic factors (i.e. ventilator dependency, significant INR elevation, need for renal replacement therapy, advanced grade of HE and even high PELD/MELD scores – see Table 3). Despite the high acuity of our patients, our results, with patient and graft survival rates of 94% and 88%, respectively, are among the best reported to date in the literature.

One risk factor that distinguishes our patient cohort from those at other centres; however, is patient age at presentation (most of our patients were more than 3 year old). Age (specifically <3 years) was a relevant prognostic factor in our experience. The two youngest patients in our series (4 months and 1.5 years old), although still surviving 23 and 11 months after the operation, developed significant, irreversible neurological complications compromising the rest of their life. Similar experiences have been reported by other authors [2,12,25]. In this critically ill population, some authors have advocated the use of mild hypothermia [26] and others, the use of intracranial pressure monitoring aimed at maintaining a mean cerebral perfusion pressure ≥50 mmHg in order to avoid irreversible neurological injury [3]. We, however, did not employ either of these modalities. For each of these two patients, the preoperative neurological status was not so severe as to represent a contraindication to LT. Potentially, the infant with PALF and high-grade encephalopathy *in the absence of* significant cerebral oedema may represent a unique subgroup at risk for post-transplant neurological sequelae even following technically successful LT and therefore may be considered as a contraindication to LT. With an experience of only two patients, however, this is only speculation. While the eventual outcome was suboptimal in these two cases, presented with the same scenarios today, we would transplant these children again.

We believe one of the primary factors accounting for our excellent survival rates, as also reported by Dhawan *et al.* [5] is the optimal perioperative management provided by an experienced paediatric ICU. To this end, the use of liver assist devices such as MARS® may have played a fundamental role in our reaching such good results. Several extracorporeal liver assist systems with hepatocytes of differing sources have been reported in a small number of pilot clinical trials without convincing results [6]. Among different 'a-cellular' liver support devices, the MARS®, showed promising preliminary results in the therapeutic arsenal for ALF in adult patients, but no sufficient data exist to justify its use in children. Prior to this report, only 18 paediatric cases have been reported worldwide and most of them are anecdotal [27,28]. Our criteria for the use of a liver assist device were an INR >3 and one or more of the following: HE ≥grade II; creatinine values >3.5 mg/dl with oliguria (<0.5 ml/kg BW/h); and hepato-renal syndrome. The patients at our centre who received a MARS® treatment were clearly more ill than those who did not. Even so, therapy with MARS® made sicker patients, who otherwise might not have been listed, into suitable transplant candidates. What is more, despite this higher initial patient acuity, the results of LT in the MARS® group were comparable with the other PALF patients.

Clearly, more patients should be treated with this method and more data collected before we can draw any clear conclusion/guidelines about use of MARS. We can only state that for transplant centres plagued by long waiting times (like through much of the EuroTransplant area), the use of MARS, for the above-mentioned indications, represents a potentially beneficial bridging procedure. If the logistic arrangements, expense or time-consuming initiation process associated with MARS® are felt to be prohibitive to its use or a centre simply lacks access to MARS®, then we recommend PS as an alternative bridge to transplant.

Moreover, potentially contributing to our outstanding results may be that the grafts from DDs were of excellent quality: young donors (median age 35 years), short stay at ICU (median 3 days), normal laboratory values

without hypernatraemia and low BMI (median 22), which generally correlated with a low risk of liver steatosis.

Clearly, the transplant options available to a patient can dramatically impact upon the outcome of PALF. With the exception of the Asian countries which depend so heavily on the use of LDLT, most of the centres performed DDLT, mainly in the form of split or reduced size LT and very few utilized LDLT (Table 1). Because of the broad surgical experience of our transplant team (nearly 900 total LT over the last 7 years, Table 2), we were able to offer our PALF patients every transplant option available.

Few other centres offered the full spectrum of procedures and interestingly, even fewer clearly reported if there was a difference between one procedure and another. Only the King's college group [29] and the group in Bergamo [21] reported clearly superior results using the split procedure with 1 year patient survival rates of 93% and 86%, respectively. We performed only five split LT with less than optimal results: one patient died on POD 44, not for reasons associated with the surgical procedure (see above) and two experienced intraoperative vascular problems (see above). Four of the five split LT children are still alive, although one of them has neurological deficits.

It is widely acknowledged that timely access to organs for patients with ALF [UNOS Status 1/ET T1 – High Urgency (HU)] varies significantly among countries and even between adjacent local areas within countries. We firmly believe that living donation should be offered to all parents of a child with ALF when the local organ procurement system is not expected to provide timely access to a suitable organ before death or irreversible brain damage [30]. Exemplifying this point, between 2004 and 2005, 108 children within the Eurotransplant-Area were registered as UNOS Status 1/ET T1 (HU) (Eurotransplant Foundation: http://www.eurotransplant.org). Eighty-four of the 108 (77%) were transplanted. The median waiting time between registration and transplantation was 9 days (range: 0–38). Sixteen children (14.8%) died while waiting and eight children (7.5%) were withdrawn from the list because of spontaneous recovery. In our region of Europe, the situation has grown worse over time. At present, the most reliable timely option at our centre for transplantation of a patient with PALF is LDLT. In this regard, several reports have shown that patients with ALF whether idiopathic, drug or toxin-induced or acute exacerbation of chronic liver disease (e.g. Wilson's disease) can be well served by LDLT [31–35].

The adoption of LDLT as an option for children suffering from ALF has met with some reluctance because of the potential pressure on the LD imparted by the imminence of the child's death. Nonetheless, resistance to LDLT in such cases has gradually diminished, because the procedure's life-saving potential has come to far outweigh any ethical dilemma and possible constraints resulting from the brevity of time for psychological evaluation of donor and family. Patient survival rates after LDLT for PALF vary between 59% and 73% in different series and are significantly worse than LDLT for other diseases. Graft survival rates ranging between 50% and 60% are also worse in ALF than those for children with other indications for LT [20,31,32]. Nevertheless, graft survival for LDLT is still better than DDLT in cases of ALF [36]. The paediatric survival results appear inferior when compared with adult patients who have undergone LDLT for HU situations. The reasons for the disparity are unclear, but could be related to the difference in aetiologies (e.g. long-lasting unknown hepatitis viral infection), the pattern of postoperative complications or the incidence of rejection (i.e. refractory acute and ductopenic rejection) [34].

In our single-centre experience with almost 200 LDLTs, we performed this operation in only four children (three were 4 years old and one was 1.5 years old), three of them had hepatitis of unknown origin and one had paracetamol intoxication. All four children were in very poor general condition: three with grade III HE and one with grade IVa HE, all four needed ventilator support, two of them had a low grade brain oedema, median INR was 2.5 (range: 1.44–3.52). Three of them received a MARS® treatment. After a median waiting time of 2 days following listing, all patients were successfully transplanted by means of left lateral LDLT. One of them developed a HAT at POD 1 and lost his graft. He was re-transplanted at POD 2 with a left lateral split graft. All children survived. The child who was re-transplanted developed a secondary biliary cirrhosis of unknown origin (e.g. ductopenic rejection like that reported by Uemoto *et al.* [34]) and one child unfortunately developed irreversible neurological damage.

Although our series of LDLT for PALF is small, our results in this subgroup compare quite favourably to those reported in the literature [1 year patient survival rates after LDLT for PALF ranging between 62% and 67% (see also Table 1)].

Conclusion

Children with ALF treated with LT at our centre enjoy excellent 1- and 5-year graft and patient survival rates. The combination of experienced paediatric ICU management preoperatively and postoperatively, the application of new liver support devices, and the capacity to offer both living and DD transplant alternatives in a timely fashion represent the best formula to achieve optimal results in children with ALF.

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References

1. Wiesner RH. MELD/PELD and the allocation of deceased donor livers for status 1 recipients with acute fulminant hepatic failure, primary nonfunction, hepatic artery thrombosis, and acute Wilson's disease. *Liver Transpl* 2004; **10**(Suppl. 2): S17.
2. Lee WS, McKiernan P, Kelly DA. Etiology, outcome and prognostic indicators of childhood fulminant hepatic failure in the United kingdom. *J Pediatr Gastroenterol Nutr* 2005; **40**: 575.
3. Goss JA, Shackleton CR, Maggard M, *et al.* Liver transplantation for fulminant hepatic failure in the pediatric patient. *Arch Surg* 1998; **133**: 839.
4. Baliga P, Alvarez S, Lindblad A, Zeng L. Posttransplant survival in pediatric fulminant hepatic failure: the SPLIT experience. *Liver Transpl* 2004; **10**: 1364.
5. Dhawan A, Cheeseman P, Mieli-Vergani G. Approaches to acute liver failure in children. *Pediatr Transplant* 2004; **8**: 584.
6. Baker A, Alonso ME, Aw MM, Ciocca M, Porta G, Rosenthal P. Hepatic failure and liver transplant: Working Group report of the second World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2004; **39**(Suppl. 2): S632.
7. Bhaduri BR, Mieli-Vergani G. Fulminant hepatic failure: pediatric aspects. *Semin Liver Dis* 1996; **16**: 349.
8. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet* 1993; **342**: 273.
9. Chan PC, Chen HL, Kong MS, *et al.* Factors affecting the mortality of pediatric fulminant hepatic failure in relation to hepatitis B virus infection. *J Gastroenterol Hepatol* 2005; **20**: 1223.
10. Ozcay F, Baskin E, Ozdemir N, Karakayali H, Emiroglu R, Haberal M. Fulminant liver failure secondary to mushroom poisoning in children: importance of early referral to a liver transplantation unit. *Pediatr Transplant* 2006; **10**: 259.
11. Squires RH Jr, Shneider BL, Bucuvalas J, *et al.* Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. *J Pediatr* 2006; **148**: 652.
12. Rivera-Penera T, Moreno J, Skaff C, McDiarmid S, Vargas J, Ament ME. Delayed encephalopathy in fulminant hepatic failure in the pediatric population and the role of liver transplantation. *J Pediatr Gastroenterol Nutr* 1997; **24**: 128.
13. Devictor D, Tahiri C, Rousset A, Massenavette B, Russo M, Huault G. Management of fulminant hepatic failure in children – an analysis of 56 cases. *Crit Care Med* 1993; **21**(Suppl. 9): S348.
14. Rakela J, Lange SM, Ludwig J, Baldus WP. Fulminant hepatitis: Mayo Clinic experience with 34 cases. *Mayo Clin Proc* 1985; **60**: 289.
15. Rakela J, Mosley JW, Edwards VM, Govindarajan S, Alpert E. A double-blinded, randomized trial of hydrocortisone in acute hepatic failure. The Acute Hepatic Failure Study Group. *Dig Dis Sci* 1991; **36**: 1223.
16. Shneider BL, Suchy FJ, Emre S. National and regional analysis of exceptions to the Pediatric End-Stage Liver Disease scoring system (2003–2004). *Liver Transpl* 2006; **12**: 40.
17. Psacharopoulos HT, Mowat AP, Davies M, Portmann B, Silk DB, Williams R. Fulminant hepatic failure in childhood: an analysis of 31 cases. *Arch Dis Child* 1980; **55**: 252.
18. Ware AJ, D'Agostino AN, Combes B. Cerebral edema: a major complication of massive hepatic necrosis. *Gastroenterology* 1971; **61**: 877.
19. Ee LC, Shepherd RW, Cleghorn GJ, *et al.* Acute liver failure in children: a regional experience. *J Paediatr Child Health* 2003; **39**: 107.
20. Emre S, Schwartz ME, Shneider B, *et al.* Living related liver transplantation for acute liver failure in children. *Liver Transpl Surg* 1999; **5**: 161.
21. Pinelli D, Spada M, Lucianetti A, *et al.* Transplantation for acute liver failure in children. *Transplant Proc* 2005; **37**: 1146.
22. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; **97**: 439.
23. Bernuau J, Goudeau A, Poynard T, *et al.* Multivariate analysis of prognostic factors in fulminant hepatitis B. *Hepatology* 1986; **6**: 648.
24. Kelly D. Liver transplantation. In: Science B, ed. *Disease of the Liver and Biliary System in Children*. Oxford: Blackwell Science, 1999: 293.
25. Devictor D, Desplanques L, Debray D, *et al.* Emergency liver transplantation for fulminant liver failure in infants and children. *Hepatology* 1992; **16**: 1156.
26. Jalan R, Olde Damink SW, Deutz NE, Hayes PC, Lee A. Moderate hypothermia in patients with acute liver failure and uncontrolled intracranial hypertension. *Gastroenterology* 2004; **127**: 1338.
27. Tissieres P, Sasbon JS, Devictor D. Liver support for fulminant hepatic failure: is it time to use the Molecular Adsorbents Recycling System in children? *Pediatr Crit Care Med* 2005; **6**: 585.
28. Wigg AJ, Padbury RT. Liver support systems: promise and reality. *J Gastroenterol Hepatol* 2005; **20**: 1807.
29. Deshpande RR, Bowles MJ, Vilca-Melendez H, *et al.* Results of split liver transplantation in children. *Ann Surg* 2002; **236**: 248.
30. Reding R. Is it right to promote living donor liver transplantation for fulminant hepatic failure in pediatric recipients? *Am J Transplant* 2005; **5**: 1587.

31. Liu CL, Fan ST, Lo CM, *et al.* Live donor liver transplantation for fulminant hepatic failure in children. *Liver Transpl* 2003; **9**: 1185.
32. Liu CL, Fan ST, Lo CM, Wong J. Living-donor liver transplantation for high-urgency situations. *Transplantation* 2003; **75**(Suppl. 3): S33.
33. Chen CL, Fan ST, Lee SG, Makuuchi M, Tanaka K. Living-donor liver transplantation: 12 years of experience in Asia. *Transplantation* 2003; **75**(Suppl. 3): S6.
34. Uemoto S, Inomata Y, Sakurai T, *et al.* Living donor liver transplantation for fulminant hepatic failure. *Transplantation* 2000; **70**: 152.
35. Tamura S, Sugawara Y, Kishi Y, Akamatsu N, Kaneko J, Makuuchi M. Living-related liver transplantation for Wilson's disease. *Clin Transplant* 2005; **19**: 483.
36. Mack CL, Ferrario M, Abecassis M, Whitington PF, Superina RA, Alonso EM. Living donor liver transplantation for children with liver failure and concurrent multiple organ system failure. *Liver Transpl* 2001; **7**: 890.
37. Errard V, Otte JB, Sokal E, *et al.* Impact of surgical and immunological parameters in pediatric liver transplantation: a multivariate analysis in 500 consecutive recipients of primary grafts. *Ann Surg* 2004; **239**: 272.
38. Broering DC, Mueller L, Ganschow R, *et al.* Is there still a need for living-related liver transplantation in children? *Ann Surg* 2001; **234**: 713.
39. Jain A, Mazariegos G, Kashyap R, *et al.* Pediatric liver transplantation. A single center experience spanning 20 years. *Transplantation* 2002; **73**: 941.