Transpl Int (2004) 17: 562–573
DOI 10.1007/s00147-004-0771-y

REVIEW ARTICLE

Jean-Bernard Otte

Paediatric liver transplantation—a review based on 20 years of personal experience

Received: 6 April 2004
Accepted: 7 June 2004
Published online: 5 November 2004

This review was presented as the first ELTA Honorary Lecture, ESOT meeting, Venice, 24 September 2003, "Pediatric liver transplantation: from 90% mortality to 90% survival".

J.-B. Otte
Unité de Chirurgie pédiatrique-Service de Transplantation Abdominale, Université Catholique de Louvain, Cliniques Saint-Luc, Avenue Hippocrate 10, 1200 Brussels, Belgium
E-mail: otte chex.ucl.ac.be
Tel.: +32-2-7641401
Fax: +32-2-7648954

Abstract The natural history of most liver diseases requiring liver replacement in children is well known, and the potential of this therapy has been ascertained regarding life expectancy, which currently exceeds 90% in the long term. The timing of liver transplantation must be anticipated, to reduce the physical, psychological and mental impact of chronic liver diseases. Several studies show evidence that the best long-term results with regard to patient and graft survival are obtained with grafts procured from relatively young donors. Since the shortage of post-mortem liver donors will most likely worsen, further development of live, related-donor transplantation can be expected. The main progress to come will concern immunosuppression, taking advantage of the immunological privilege of the liver. Protocols are under development for induction of operational tolerance.

Keywords Children · Liver transplantation · Indications · Survival · Medical complications · Immunosuppression

History

The history of paediatric liver transplantation cannot be dissociated from the name of Thomas E. Starzl, whose pioneering and ever-continuing efforts contributed more than anyone else's to what has become a routinely successful procedure [1, 2]. I had the unique privilege to be his research fellow during my 3rd-year surgical residency (1965–1966).

His first attempt, performed in 1963 in a child with biliary atresia, failed [3]. Four of the eight children that received transplants in 1967 survived beyond 1 year; one is still alive, in perfect clinical condition, off immunosuppression for >17 years (T.E. Starzl, personal communication). Cyclosporine, introduced in 1980, allowed the long-term survival of the majority of children that had received transplants [4]. After its transfer to the University of Pittsburgh in 1981, the liver programme of T.E. Starzl expanded impressively, with 808 children (<18 years) receiving a transplant between March 1981 and April 1998 [5].

In Europe, liver transplantation in a 10-month-old child with biliary atresia was attempted in Cambridge, UK, by Sir Roy Calne [6] in June 1968; the child died during surgery.

In continental Europe, we performed, in March 1971, the first successful liver transplantation in an 18-month-old child with biliary atresia [7]. Our programme really started in 1984, on a multidisciplinary paediatric basis, after the transfer of our university hospital from Leuven to Brussels. The first four children are still alive, having reached 20 years of post-transplant survival. From 1984 to 2003 our group performed liver transplantation in 593 children (<15 years), including 120 patients who re-

ceived a live, related-donor transplant. Most of those children were referred from abroad. Prof. Daniel Alagille [8] was the first to put his trust in our group. In 1985 we started a 3-year collaboration while awaiting the implementation of a liver programme in HôpitalBicêtre, Paris. We were honoured by the collaboration with this distinguished paediatric hepatologist, who was an internationally recognised expert in the field. Through his recommendations he gave the impetus to many paediatricians from other countries to entrust their patients to our team.

The first international symposium on paediatric liver transplantation was organised in Brussels in October 1986 [9]. Eight teams that had performed at least 20 operations were invited to present their results (Table 1). These centres (except Denver/Pittsburgh) started their experience in the early 1980s, when cyclosporine became available. One-year patient survival rates ranged between 57% and 83%. In the following years excellent programmes were developed in a number of centres in Europe, North America, Japan and South Africa.

Current status

Results obtained during the past two decades are the consequence of substantial progress made in all areas involved in liver transplantation, including surgical techniques, selection and preparation of candidates, immunosuppression and medical management. We review these areas thereafter.

Technical developments regarding the donor graft

The shortage of size-matched, small paediatric donors gave an impetus to the development of new techniques allowing the transplantation of segmental liver grafts procured from larger donors, either adolescents or adults; indeed, the majority of liver candidates are infants and young children [10, 11]. In the "reduced-size liver" technique, originally described by Bismuth and Houssin [12], the donor liver is cut down to the left lateral segment (or the left lobe); this innovative technique was validated in the late 1980s [13, 14] and used worldwide. It was criticised because of the potential prejudice to adult recipients, since it does not increase the liver pool; it has become obsolete except in particular circumstances.

Table 1 First series of liver transplantation in children, international symposium, Brussels 11–12 October 1986

Centres	Interval	Number	1-Year patient survival (%)
Denver	1967–1980	86	30
Pittsburgh	1980–1986	265	70
Cambridge	1983–1986	35	43
Boston	1984–1986	23	59
Dallas	1984–1986	44	74
Hanover	1978–1986	35	66
Ucla	1983–1986	38	70
Brussels	1984–1986	30	83
Minneapolis	1984–1986	35	65

The concept of the "split-liver graft" was described in the late 1980s [15, 16, 17, 18] and validated in the 1990s [19, 20, 21]. By the division of the donor liver structures and parenchyma in such a way as to provide two grafts prepared from one single organ, this technique allows significant expansion of the liver pool. Indeed, it is estimated that 20%–25% of post-mortem donor grafts can be safely divided [22, 23]. Usually, the liver is divided along the umbilical scissure between the left lateral segment (Couinaud's segments II and III) and an extended right lobe (Couinaud's segments IV–VIII), which are transplanted into a child and an adult recipient, respectively. Alternatively, the liver can be divided along the main scissure if the size of the paediatric recipient requires a greater liver mass or when both recipients are adults [24]. The splitting technique is complex and can be performed in two ways. In the ex situ technique [17, 18, 22] the division of the liver on the back table entails a risk of re-warming after core cooling and procurement. Experience with live liver donors led to the development of the in situ technique by the Hamburg group [25], soon followed by the UCLA group [23, 26]. In the in situ technique the liver division is performed as the first stage of the multi-organ procurement in a heart-beating, post-mortem donor. The advantages of the latter technique are the perfect haemostasis of the cut section and an optimal preservation and timing that facilitate graft sharing between distant transplant centres. The good results provided by both techniques have contributed to reduce the waiting lists [27, 28]. Unfortunately, the potential of the procedure is under-exploited due its complexity and the lack of experience of many centres [29].

Live, related-donor liver transplantation

Persisting post-mortem organ shortage justified its development in USA [30], Europe [19, 31, 32] and Japan [33]. The first success was obtained by Strong et al. in Australia [34]. Procurement of the left lateral segment is a relatively straightforward procedure that provides enough liver mass for most paediatric liver recipients. The risk of lethal complications in the donor is minimal; to the best of our knowledge [35, 36] there have been two postoperative deaths, one in Europe [31] and one in the USA [37], out of some 2000 cases, which represents a risk of dying of approximately 1:1000. If needed, the procurement can be extended to the full left lobe or even the right lobe for bigger recipients, although the latter

type of procurement is more complex and significantly more risky for the donor [36].

The prerequisites for a live, related-donor liver transplantation programme are a protocol approved by the local ethics committee (or the institution review board) [30] and strictly followed, a stringent selection of the donors offering to donate, in order to exclude any extra-operative risk, and large experience with all types of liver resection and transplantation techniques. Respecting the donor's autonomy is of paramount importance. Each potential donor should be offered three options: living donation if such is his/her confirmed decision, listing on the post-mortem waiting list, or the latter option with the possibility to donate, should the recipient condition deteriorate before a post-mortem graft is available.

In order to respect the donor's autonomy, it is the responsibility of the transplant professionals to develop efficient programmes of post-mortem liver donation to offer the parents a realistic choice. Live-donor liver transplantation can only be justified if all available resources for cadaveric transplantation (including split livers) are fully exploited [36]. Assessing a candidate for donation is a team approach, committing all members to making sure that the decision to donate is made freely. The donors must receive detailed, honest and complete information regarding the risks and benefits and the specific centre experience. Donors deserve attention, compassion, empathy and psychological support from the medical and nursing staff throughout the entire procedure of assessment, donation and follow-up. Donors must be treated as patients, with assiduous attention to alleviation of postoperative pain [36].

Technical developments regarding the recipient

Modifications to the original technique of orthotopic liver transplantation described by Starzl [1] aimed to reduce surgical complications and cope with peculiar anatomic situations. Segmental grafts require the preservation of the recipient vena cava with piggyback implantation [38, 39] and wide anastomosis of the left hepatic vein ($\pm$ the median hepatic vein) to allow free venous drainage [40].

Arterial thrombosis plagued the early days of paediatric liver transplantation [41, 42]; it was a major cause of patient morbidity and graft loss. Its incidence was drastically reduced by several measures, including a meticulous, (semi)-microscopic reconstruction technique, a low haematocrit ($\pm 30\%$) during the early post-transplantation period, anti-platelet agents and a careful echographic follow-up. Combination of these preventive measures reduces the incidence of this dreadful complication to a low $<2\%$ after transplantation of a left lateral segment from a live donor [36, 43].

Portal vein thrombosis has been observed after all types of liver grafts; significant risk factors are patient's low weight and small size of the portal vein, particularly in biliary atresia, which is often associated with hypoplasia of the portal vein [44]. Its prevention depends primarily on appropriate surgical technique and the liberal use of a jump venous allograft or autograft implanted on the superior mesenteric vein. Early portal thrombosis leads to graft loss if not repaired immediately. Late thrombosis leads to extrahepatic portal hypertension, which is best corrected by a jump venous graft interposed between the superior mesenteric vein and the extrahepatic portion of the left portal vein ("meso-Rex shunt") [45].

Biliary complications are frequent in paediatric liver transplantation. Anastomotic strictures seem to occur more frequently in left split grafts and left lateral live liver segments [46] (the most likely reason being ischaemia of the cut section of the left hepatic bile duct). The aetiology of intrahepatic biliary strictures is multifactorial: prolonged cold ischaemia, insufficient rinsing and cooling of the intrahepatic biliary tree due to the viscosity of the UW solution, unsuspected arterial thrombosis, immunological and viral (CMV) causes; all these can play a role [47]. Biliary strictures may become clinically manifest any time after transplantation, even in the long term (>15 years). Clinicians must pay great attention to persisting anomalies of the cholestasis enzymes, the slightest bout of suspected or obvious cholangitis and/or the dilatation, even discrete, of the biliary tree on the ultrasound follow-up.

Any of these observations is a compelling reason for investigating the bile ducts. Anastomotic strictures may not be left alone. According to the local expertise, percutaneous trans-hepatic dilatation [48] or straight surgical correction (which is our preferred option) should be performed promptly. Intrahepatic strictures are a therapeutic challenge. If they are not accessible to percutaneous dilatation, they lay the ground for repeated bouts of cholangitis, which can lead to biliary cirrhosis and graft loss. Long-term, indefinite, intermittent antibiotic prophylaxis and ursodeoxycholic acid are indicated for slowing down this process.

Selection of candidates and preparation before transplantation

The excellent results obtained for years justify the early performance of liver transplantation without waiting for the end-stage of liver disease. The optimal preparation before transplantation requires a multidisciplinary approach [49], including appropriate formulation [50] with either oral or enteral administration or, if needed, parenteral nutrition, fat-soluble vitamins supplementation in cholestatic children, control of bleeding oesophageal

or gastric varices [51] and treatment of ascites and infections.

Indications

Cholestatic diseases

In *biliary atresia* a consensus for a sequential strategy was accepted more than 10 years ago [52]. Affected neonates require early surgery, hopefully before the age of 6 weeks, consisting of a standard Kasaiporto-enterostomy with a long (> 50 cm) Roux-en-Y loop [53]. Should it fail to restore bile flow, a redo is no longer justified; instead, the infant should be referred promptly to an experienced liver transplant centre. When bile flow has been re-established, liver replacement will be required sooner or later from the complications of the underlying liver disease: evolution toward biliary cirrhosis; repeated bouts of cholangitis; portal hypertension; growth failure; poor quality of life related to intractable pruritus, hepatopulmonary syndrome, which is reversible after transplantation [54, 55]. Only a minority of patients will reach adulthood without liver transplantation [56].

In *progressive familial intrahepatic cholestasis* (PFIC), previously named Byler's disease, an external biliary diversion can control cholestasis in non-cirrhotic children [57, 58]; however, a stoma can be a psychological hurdle for schoolchildren. Otherwise, liver replacement can be required by intense jaundice and pruritus, growth failure and, occasionally liver failure and complications of portal hypertension.

In *syndromic ductular paucity* ("Alagille's syndrome"), liver insufficiency is uncommon. Liver replacement should be considered in cases of poor quality of life related to jaundice, pruritus not responding to medical therapy, multiple xanthomas, or, more rarely, because of complications of liver cirrhosis and portal hypertension. Contrary to early reports, high right ventricular pressures do not contraindicate liver transplantation [59].

In-born errors of metabolism

A *When the enzyme deficit is limited to the liver* (Crigler–Najjar's disease, Wilson's disease, alpha-1 antitrypsin deficiency, urea-cycle disorders, primary hyperoxaluria type I...) cure is complete after liver transplantation if it is performed early enough to prevent irreversible extrahepatic complications (such as neurological complications in Crigler–Najjar's disease). If the liver is normal but for the absence of an enzyme, the indications for liver replacement are based on poor quality of life, e.g. in Crigler-Najjar's disease, where phototherapy becomes excessively constrainingin the growing child [60], or on extrahepatic complications, as in primary hyperoxaluria type I (indication for combined liver–kidney transplantation, in order to avoid systemic oxalosis, when GFR falls to < 50 ml/min) [61]. When the enzyme deficit leads to liver cirrhosis (alpha-1 antitrypsin deficiency, tyrosinaemia, Wilson's disease...), liver failure is the indication for transplantation. However, Wilson's disease is commonly controlled by medical treatment, except in cases of fulminant presentation and, occasionally, severe liver disease [62]. Indication for liver transplantation in tyrosinaemia has become uncommon since the introduction of NTBC as an enzyme inhibitor [63, 64], although prevention of hepatocellular cancer is not yet guaranteed in the long term.

B *When the enzyme deficit is generalised* the indications for liver replacement are complex and need discussion on a case-by-case basis.

Homozygous familial hypercholesterolemia is cured by liver transplantation [65].The time to proceed is dictated by the response to medical treatment (statins) but should precede the onset of cardiovascular complications. Improved long-term survival in *cystic fibrosis* has led to an increased incidence of extrapulmonary complications. Liver transplantation will tackle the complications of cholestatic cirrhosis without sparing the patient continued respiratory care. Improvement of the nutritional status post-liver transplantation may slow down the evolution of the lung disease, although it is still a matter of debate [66].

Mitochondrial respiratory-chain disorders may lead to neonatal or late liver failure, requiring liver transplantation. In rare cases the disease is restricted to the liver and the patient is cured after transplantation. More frequently, other organs are involved; therefore, pretransplant assessment should aim to rule out neuromuscular disease [67].

In *glycogen storage disease type I*, liver transplantation is indicated when the dietary treatment fails, with poor metabolic balance and growth retardation [68], or when hepatic adenomas develop, with the possibility of neoplastic transformation [69]. It allows a long-lasting improvement in quality of life and correction of the growth failure, although it does not seem to prevent segmental glomerulosclerosis in the long term [68].

In *glycogen storage disease type IV*, death caused by heart failure due to persistence of myocardial deposits of amylopectin has been observed after liver transplantation [70, 71]. On the other hand, resorption of such deposits has been described in long-term survivors [72], which has been attributed to microchimerism [73]. The benefit resulting from liver replacement is limited in rare diseases such as *organic acidurias*, although it can be

spectacular regarding growth and quality of life, as we observed in one child; however, late renal insufficiency is not prevented.

Fulminant liver failure

Liver transplantation is indicated in children presenting with hepatic encephalopathy associated with a decrease in the level of factor V to below 25% [74].The survival rate is in the range of 70%, without irreversible neurological complications if a liver graft can be obtained promptly. In this regard, a large pool of potential donors with an efficient organ allocation system is essential for providing a graft within a short time; such is the case with Eurotransplant (approximately 120 million inhabitants; median waiting time of 24 h for a patient registered on the high-urgency waiting list).

Malignant liver tumours

Unresectable *hepatocellular cancer* is a poor indication for liver transplantation, with a survival rate as low as in adults (< 20% at 5-year post-transplantation), except for the incidental tumour associated with a chronic, non-viral liver disease. Therefore, selection of candidates must remain stringent inasmuch as no efficient chemotherapy is available. The issue is completely different for *hepatoblastoma*, which is the most frequent malignant liver tumour in children. The cure rate of hepatoblastoma has been dramatically improved since the introduction of cisplatin [75, 76], although complete tumour resection remains a prerequisite for cure. Liver transplantation is a validated option for tumours that remain unresectable after completion of chemotherapy [77]. Lung deposits at presentation do not contraindicate liver transplantation if they clear after chemotherapy; any residue should be surgically resected before transplantation is performed. Extent into the major venous branches was the only statistically significant prognostic factor we found in a multivariate analysis of the world experience, although it does not contraindicate liver transplantation if radical excision is possible. The 6–10-year, disease-free survival rate after primary transplantation is in the range of 80%, similar to that of patients who can be treated with a partial liver resection [76, 77].

Life expectancy

The long-term (> 10 years) life expectancy approaches 80% in experienced centres. The actuarial survival rate at 20 years of our cohort of 593 children (< 15 years) that received transplants between 1984 and 2003, all indications included, is 78.6%. Like other centres that started paediatric liver transplantation in the early 1980s, we experienced a learning phenomenon, with a 5-year actuarial survival rate of 96.8% for the last 83 cases (2001–2003) (Fig. 1). The most spectacular progress was achieved in infants and young children (< 1 year), with long-term life expectancy similar to or even higher than in older children (Fig. 2); the best results are obtained with live, related-donor liver transplantation in both age categories. The overall patient survival rate in live related transplantation was 86% for the first 57 cases (1993–1997) and 96% for the following 63 cases (1998–2003), with a low (< 3%) re-transplantation rate. The actuarial survival rate at 10-years was 90.3% for the 107 children that had received a transplant from a live, related donor (1993–2002), compared with 83.4% for the 142 children who received a post-mortem liver transplant during the same period (Fig. 3). The difference was even more striking when the life expectancy was calculated from the time of registration on the waiting list (which should be the rule since this is what matters for patients and parents): the 10-year actuarial survival rates were 87.8% and 71.7% for the recipients of a live, related-donor liver graft ($n = 110$) or of a post-mortem graft ($n = 165$), respectively. Differences of the same magnitude were observed for elective cases. Several centres have published similar results.

Both split-liver transplantation and live, related-donor transplantation contributed to alleviate mortality of children on waiting lists [23, 28], but a debate persists regarding the best donor grafts to use in infants. Limiting the upper donor age is common sense for young paediatric recipients but is somehow arbitrary (< 40–50 years?), both for assuring graft quality and limiting the age difference between donors and recipients. Although the Bergamo group [78] reported that donor age > 50 years did not impact on the 3-year patient and graft survival rates, the use of livers procured from elderly

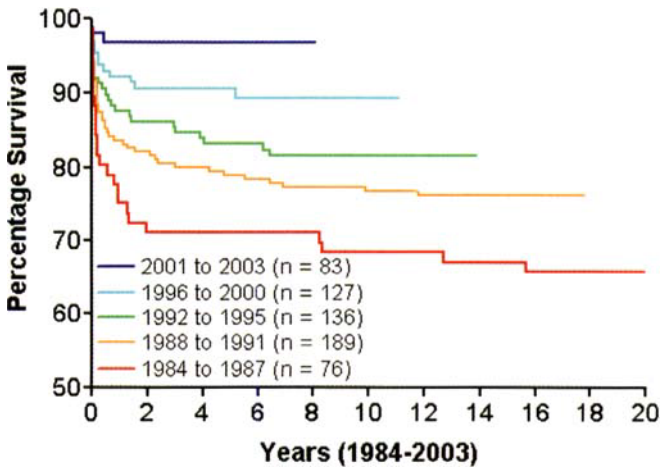

Fig. 1 Learning curve (1984–2003). Some children that have undergone re-transplantation appear on more then one curve

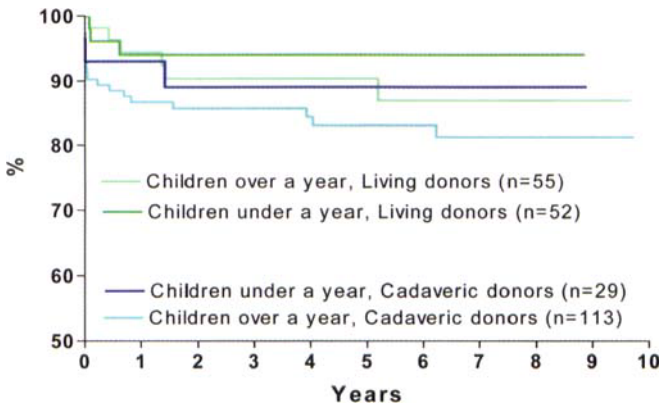

Fig. 2 Survival curves of children < 1 year old, compared with children > 1 year old; living donors versus post-mortem donors (1993–2002)

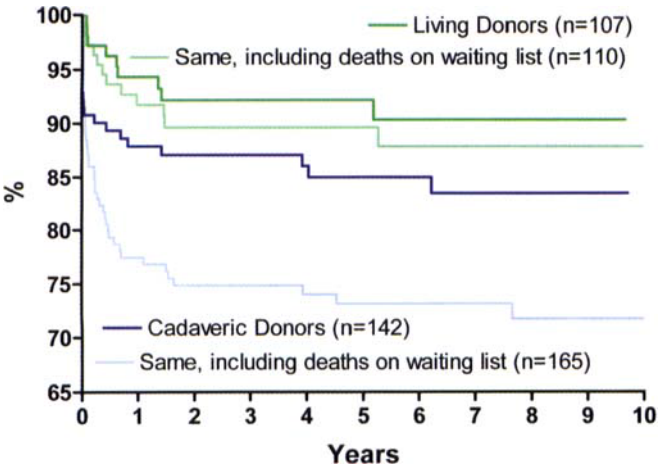

Fig. 3 Survival curves of recipients of a live, related-donor transplant compared with those with a post-mortem donor graft. Survival calculated from the day of transplantation versus from the time of registration (1993–2002)

donors is controversial in young children and infants who represent the majority of paediatric candidates. Indeed, a 3-year follow-up is much too short to assert that older donor age will not have an impact on the very long-term (> 30 years) outcome that should be the aim in paediatric recipients. Indeed, the analysis of the UNOS data (1992–1997) [79] showed a significantly ($P < 0.001$) higher graft survival rate in children who had received their graft from paediatric-aged donors than in children who had received their graft from > 18-year old donors (81% versus 63%). The Groningen group [80] also observed that older donor age was a risk factor for late graft loss. For recipients aged < 2 years, the analysis of the US Scientific Registry of Transplant Recipients database disclosed that live, related-donor transplantation provides superior graft survival then cadaveric transplants, whether full-size or split grafts [81]. Independently of the donor age, the quality of the graft parenchyma makes the fundamental difference between partial grafts derived from living donors (LDs) and split-liver transplants (SLTs), as revealed by the specific patterns of complications and the incidence of primary non-function (PNF) [23]. In this report about their experience with in situ split-liver transplantation, acquired between September 1991 and February 2003, the UCLA group compared the incidence of complications and the patient and graft survival rates observed in 93 paediatric recipients who received a split graft [left lateral segment (SLT-LLS)] with those observed in 43 recipients of an LD graft (LD-LLS) and in 207 recipients of paediatric whole-organ transplants (FSs). The incidence of biliary complications among SLT-LLS, LD-LLS and FS was similar (9%, 12%, and 10%, respectively). Hepatic artery thrombosis was observed in 7%, 18%, and 13%, respectively. Portal vein thrombosis occurred in 8% of SLT-LLS and 11% of LD-LLS. PNF was significantly increased among SLT-LLS recipients: 8.5% compared with 2% in LD-LLS and 3.4% in FS (all grafts required re-transplantation). The increased incidence of acute complications among SLT-LLS recipients resulted in a lower graft survival curve: the 3-year graft survival rates were 64%, 71%, and 73% in recipients of SLT-LLS, LD-LLS, and FS, respectively. Recipient survival for each type of graft followed a similar trend, with a 3-year recipient survival rate of 75% in SLT-LLS, compared with 84% for LD-LLS and 81% for FS. Comparison of overall recipient survival between graft types, when stratified by UNOS status at transplantation, revealed no significant differences. The absence of significant differences in patient and graft survival in this otherwise remarkable series might be attributed to the less-than-optimal results obtained with LDs.

Our group has showed that liver transplantation (LT) from a live donor (LD) provides significantly better graft survival than transplantation from a post-mortem donor (PMD) [82].The outcome was compared between 100 LDs and 136 PMDs performed between July 1993 and April 2002. The median recipient age (range) at LT was 1.0 year (0.4–13.1) in the LD group versus 2.4 years (0.2–14.9) in the PMD group. The actuarial 5-year patient survival rate was 92% in the live, related-donor (LRD) group versus 85% in the PMD group [not significant (NS)]. The 5-year graft survival rate was 89% in the LDs versus 77% in the PMDs ($P = 0.027$). The re-transplantation rate was 3% in the LD group versus 11% in the PMD group ($P = 0.022$). The rate of vascular complications (arterial or portal thrombosis) leading to graft or patient loss was 2% in the LD group versus 7% in the PMD group.

Taking the published results of live, related-donor liver transplantation and post-mortem liver transplantation (whatever the technical modalities) together, one

may conclude that live, related-donor liver transplantation (LRLT) from a parental donor offers the ideal option to the paediatric recipient with regard to the long-term outlook. This strategy is supported by the experience that donation of a left lateral segment by a healthy adult is unquestionably the safest type of liver donation [36, 83].

Except for that for malignant tumours, long-term life expectancy does not depend any longer on the disease's requiring transplantation. Results obtained in biliary atresia in 1993–2002 [84] were among the best [10-year survival rate of 95.6% for living donors ($n=72$) and 89.2% for post-mortem donors ($n=76$) (Fig. 4)]. Combined results of porto-enterostomy and liver transplantation have drastically improved the outcome of biliary atresia, which was always lethal in early childhood less than 40 years ago [85]. In metabolic diseases, survival rate obtained in 94 children was 89.2% beyond 10 years; the best results were obtained in alpha-1 antitrypsin deficiency (all eight children that had been given transplants by our group and all 21 children that had received transplants at King's College [86] survived) and in PFIC (10-year survival rate of 97.4% in 39 children).

In a multivariate analysis performed on 500 consecutive children that had received a transplant between 1984 and 2000 [11], only three factors were found to be independently correlated with better patient survival: year of transplantation (learning curve effect; $P=0.001$), pre-transplant diagnosis ($P<0.001$, worst results for liver tumours) and ABO incompatibility ($P<0.001$). Similarly, three factors were independently correlated with better rejection-free graft survival: tacrolimus as primary immunosuppressant ($P<0.001$), a negative T-cell cross-match ($P=0.016$) and younger age of the donor ($P<0.001$); the meaning of the impact of the young age of the donor on the rejection rate is unclear.

Medical complications

The drawback of heavy immunosuppression is a high incidence of infections in debilitated children and a significant risk of lymphoproliferative disorder (PTLD). Improvement of nutritional status before transplantation and reduction of immunosuppression, including reduction, withdrawal or even withholding of steroids (see below) have diminished the incidence and severity of bacterial, viral and mycotic infections. Although the frequency of EBV-related PTLD remains a concern, mostly in EBV-negative recipients [87, 88, 89], major progress has been achieved in its early detection and follow-up (quantitative RNA and counting of EBV-specific toxic CD8) and its treatment (anti-CD20 MoAb) [90]. Thanks to these measures, we have not lost any patient to PTLD for many years.

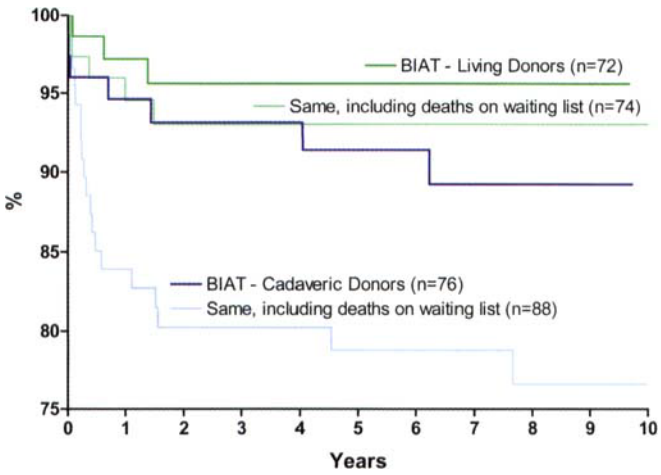

Fig. 4 Survival curves of biliary atresia patients; living donors versus post-mortem donors (1993–2002) (*BIAT* biliary atresia)

The two major immunosuppressive agents, cyclosporine and tacrolimus, incur risks of nephrotoxicity and neurotoxicity, the consequences of the latter, with regard to cognitive development, remaining poorly appreciated. Tacrolimus has emerged as the first choice in paediatric liver transplantation [11, 91]. Through experience gained during the past decade, we learned that the trough level initially recommended for tacrolimus was much too high. Currently, we keep the trough level at 10–12 ng/ml or below during the early post-transplant period and between 6 ng/ml and 8 ng/ml after 3 months post-transplantation. In the long term, beyond the first post-transplantation year, we allow the trough level to drop below the therapeutic range (<6 ng/ml) if the graft is well tolerated; more recently, we adopted a similar policy from the seventh post-transplant month. Such a strategy minimises the risk of nephrotoxicity and neurotoxicity and virtually eliminates the risk of the patient's developing insulin-dependent diabetes mellitus, in the absence of other risk factors such as cystic fibrosis. Moreover, it is likely to be favourable to the establishment of operational tolerance [92].

Whether LRLT has an immunological advantage, compared with cadaveric liver transplantation (CLT), regarding the incidence of rejection, remains controversial [93]. Toyoki et al. [94] found no difference in acute rejection incidence in the first year post-transplantation between 51 LRLTs and 37 CLTs. However, they observed a significant reduction of rejection in the LRLT group after 1 year post-transplantation and a more successful reduction of immunosuppression in this group. Other studies have confirmed that there was no difference in acute rejection [95, 96, 97]. Alonso et al. [96] observed that LRLT recipients are less likely than CLT recipients to develop steroid-resistant rejection or ductopenic rejection. Gupta et al. [98] also observed a significant reduction in chronic rejection in LRLT children.

Autoimmune hepatitis has been described after paediatric liver transplantation [99]. In our centre [100] 11 patients out of 471 (2.5%) that received transplants between 1984 and 1998 were found to have autoimmune hepatitis during their follow-up; none had had previous autoimmune liver disease. These patients had a history of steroid-dependent hepatitis with variable degree of portal and lobular inflammation, piecemeal necrosis and bridging collapse. All patients had high concentrations of IgG (median 1,365 mg/dl) and high titres of autoantibodies. They did not respond to increasing dosage of cyclosporine ($n=10$) or tacrolimus ($n=1$). Eleven received steroids (prednisolone 2 mg/kg per day, then tapered) and azathioprine (1.5 mg/kg to 2.5 mg/kg per day). AST and ALT levels of all patients had normalised within 3 months. Three patients had a mild-to-moderate relapse, with increase of ALT, thereafter. Systematic screening for autoimmune markers is recommended in children with a liver transplant. Autoimmune hepatitis should be considered in children with persisting abnormal levels of transaminases and/or showing a histological picture of "unspecific" hepatitis.

Quality of life

The survival curves of liver-transplant children remain remarkably stable beyond the first post-transplantation year (Fig. 1) in contrast to those obtained in liver-transplant adult patients, one reason being that relapse of the original liver disease is exceptional in children. The majority of children surviving >5–10 years post-transplantation are expected to enjoy a life expectancy close to normal (the current longest survival time is 37 years [101]).Therefore, studying their quality of life has become a top priority with regard to their growth, psychosocial development, academic achievement, employment and sexuality.

A comprehensive review of the literature between 1966 and 2001 has been recently published [102].

Growth retardation is a common complication of chronic liver diseases, most often related to malnutrition [49, 103]. It is corrected after transplantation, although, in some children, the growth velocity remains slower than normal for several years. A study has shown that the growth catch-up was closer to normal in children aged younger than 24 months at transplantation than in children older than that [104]. This study concluded that early transplantation of children who show growth retardation is optimal for restoration of growth potential. In diseases such as Alagille's syndrome and PFIC [105], the growth potential can be genetically limited. Post-transplantation growth catch-up is impaired by steroids; this impairment is reduced by dosing of steroids on alternate days [106] or their withdrawal [107, 108] and is avoided by steroid withholding. In a pilot study, our group has shown that induction with tacrolimus and an anti-IL2 receptor Moab allows growth catch-up to start as soon as the second semester after transplantation [109]. The administration of growth hormone is very rarely indicated in liver transplantation [110].

Cognitive development Retardation of the cognitive development is characteristic of chronic liver insufficiency; it was reported to be more common in children that had received transplants than in the general population [111], but controlled studies are lacking and specific risk factors have not been clearly identified. In one study, learning disabilities have been found in 26% of the children [111]. In contrast, our own study suggested that liver transplantation does not substantially affect schooling [112]. The mental abilities of children with liver transplants tend to improve over time [113].

Psychosocial development

Psychosocial assessments after liver transplantation have showed that 50% or more of children have adverse psychological reactions, or behavioural or emotional disturbances [114]. The observations we made in 146 patients aged 4–25 years, who had received a liver transplant 2–12 years previously, were less pejorative [112, 115].

As recommended by Fine et al. [102], multicentric longitudinal studies are required to clarify these three issues, which have an important potential impact on the quality of life.

Future directions

From the technical perspective, all types of surgical procedures seem to have been explored. The natural history of most liver diseases is well known, and the potential of liver transplantation has been ascertained with regard to life expectancy. Therefore, the timing of transplantation must be anticipated, to reduce the physical, psychological and mental impact of chronic liver diseases. Since the shortage of post-mortem donors will most likely worsen, further development of live, related-donor liver transplantation can be expected unless split-liver transplantation expands much further than currently [29]. The profile of the post-mortem donor as becoming older, and an increasing proportion of "marginal" donors, means that fewer donor livers will be available for safe splitting. However, prospective studies will be needed to confirm the superiority of live-donor transplantation with regard to quality of life, both for recipients and their families [116].

The main progress to come will concern immunosuppression. Tacrolimus is, nowadays, the first choice, both for the lower incidence of acute rejection and the lower prevalence of side effects compared with

cyclosporine [91]. In particular, the absence of cosmetic side effects of tacrolimus is of paramount importance in children, as well as the more discrete disturbance of the lipid profile. Studies performed in human renal transplantation have shown a correlation between the genetic polymorphism of CYP3A and the blood trough level of tacrolimus [117, 118]. Genetic typing of the recipient (and of the donor in liver transplantation, since the CYP3A is of donor origin) would allow a tailoring of the dosage to the patient phenotype with minimisation of the side effects, including nephrotoxicity. Indeed, it has been shown that the frequency of renal dysfunction related to calcineurin inhibitors is reduced in patients with the ABCB1 genotype of the multidrug resistance transporter [119].

Spontaneous reversibility of acute rejection, described in several animal models and occasionally observed in humans, absence of impact of acute rejection on graft survival, and operational tolerance observed in some children who discontinued immunosuppression testify to the immunological privilege of the liver. These observations have led to a significant lightening of the immunosuppressive regimens from the induction phase. Protocols of early withdrawal of steroids have been validated [108, 120]. A recent study, which still needs confirmation in a larger cohort of patients, suggests that steroid-free immunosuppression is safe with regard to the incidence of rejection, while it greatly facilitates the postoperative course and allows early growth catch-up [109]. The mandatory withdrawal of immunosuppression dictated by PTLD has revealed that immunosuppression does not have to be resumed in every patient, as observed by several groups, including ours (in our experience, the longest follow-up of such a patient off immunosuppression because of a previous PTLD is 17 years).

These observations of "operational tolerance" constituted the basis for the development of protocols of progressive withdrawal of immunosuppression in Pittsburgh [101, 121] and Kyoto [122]; complete withdrawal was successfully achieved in 19% and 38%, respectively. Besides the necessity to re-intensify the medical follow-up in patients who used to see the transplant doctor once in a while, this approach is not without risk of triggering acute rejection, which was actually seen in approximately 25% of patients enrolled in both studies, fortunately without graft loss. The ultimate evolution is the clinical application of tolerance-induction protocols in organ transplantation, as initiated at the University of Pittsburgh [123]. The early results are impressive, feeding the hope that the "holy grail " is within reaching distance.

Preliminary results obtained with hepatocyte transplantation in a few cases of metabolic diseases [124] and fulminant hepatitis [125] are encouraging. Further research is needed to confirm the long-term efficiency and define the curative or palliative role (as a bridge to liver transplantation) of this approach.

Acknowledgements The author warmly thanks all members of the multi-disciplinary team of paediatric liver transplantation at the Cliniques Saint-Luc for their skills and dedication; they played the major role in obtaining the results that form the basis of this review. Statistical analyses were performed by Doctor D. Gonze, data manager.

References

1. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the liver in humans. Surg Gynecol Obstet 1963; 117:659.
2. Starzl TE, Groth CG, Brettschneider L, et al. Orthotopic homotransplantation of the human liver. Ann Surg 1968; 168:392.
3. Starzl T. Memoirs of a transplant surgeon. The puzzle people. 1992; Pittsburgh, p 99.
4. Starzl TE, Klintmalm GB, Porter KA, Iwatsuki S, Schroter GP. Liver transplantation with use of cyclosporin A and prednisone. N Engl J Med 1981; 305:266.
5. Jain A, Kashyap R, Potdar S. Pediatric liver transplantation in 808 consecutive children: 18 years experience from a single center (abstract). Am J Transplant 2001; 1:288.
6. Calne R. Liver transplantation. Grune and Stratton, 1987.
7. Otte JB. Les transplantations d'organes. Presse Med 1972; 4:263.
8. Alagille D. [Liver transplantation in children. Where does it stand in 1986?] La transplantation hepatiquechez l'enfant. Qu'en est-il en 1986? Arch Fr Pediatr 1986; 43:589.
9. Otte JB, Starzl TE, Ascher N. Liver transplantation in children. Proceedings of the European Symposium. Transplant Proc 1987; 19:3229.
10. Noujaim HM, Mayer DA, Buckles JA, et al. Techniques for and outcome of liver transplantation in neonates and infants weighing up to 5 kilograms. J Pediatr Surg 2002; 37:159.
11. Evrard 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.
12. Bismuth H, Houssin D. Reduced-sized orthotopic liver graft in hepatic transplantation in children. Surgery 1984; 95:367.
13. Broelsch CE, Emond JC, Thistlethwaite JR, Rouch DA, Whitington PF, Lichtor JL. Liver transplantation with reduced-size donor organs. Transplantation 1988; 45:519.
14. Otte JB, de Ville de Goyet j, Sokal E, et al. Size reduction of the donor liver is a safe way to alleviate the shortage of size-matched organs in pediatric liver transplantation. Ann Surg 1990; 211:146.

15. Pichlmayr R, Ringe B, Gubernatis G, Hauss J, Bunzendahl H. [Transplantation of a donor liver to 2 recipients (splitting transplantation)—a new method in the further development of segmental liver transplantation] Transplantation einer Spenderleber auf zwei Empfanger (Splitting-Transplantation)—Eineneue Methode in der Weiterentwicklung der Lebersegment transplantation. Langenbecks Arch Chir 1988; 373:127.
16. Bismuth H, Morino M, Castaing D, et al. Emergency orthotopic liver transplantation in two patients using one donor liver. Br J Surg 1989; 76:722.
17. Broelsch CE, Emond JC, Whitington PF, Thistlethwaite JR, Baker AL, Lichtor JL. Application of reduced-size liver transplants as split grafts, auxiliary orthotopic grafts, and living related segmental transplants. Ann Surg 1990; 212:368.
18. Otte JB, de Ville de Goyet J, Alberti D, Balladur P, de Hemptinne B. The concept and technique of the split liver in clinical transplantation. Surgery 1990; 107:605.
19. Otte JB, de Ville de Goyet j, Reding R, et al. Pediatric liver transplantation: from the full-size liver graft to reduced, split, and living related liver transplantation. Pediatr Surg Int 1998; 13:308.
20. Otte JB. The availability of all technical modalities for pediatric liver transplant programs. Pediatr Transplant 2001; 5:1.
21. de Ville de Goyet J. Split liver transplantation in Europe—1988 to 1993. Transplantation 1995; 59:1371.
22. Azoulay D, Marin-Hargreaves G, Castaing D, Bismuth H. Ex situ splitting of the liver: the versatile Paul Brousse technique. Arch Surg 2001; 136:956.
23. Yersiz H, Renz JF, Farmer DG, Hisatake GM, McDiarmid SV, Busuttil RW. One hundred in situ split-liver transplantations: a single-center experience. Ann Surg 2003; 238:496.
24. de Ville de Goyet J, Otte JB. Cut-down and split liver transplantation. In: Busuttil AA, Klintmalm G (eds). Transplantation of the liver. Saunders, Philadelphia, 1996; p 481.
25. Rogiers X, Malago M, Gawad K, et al. In situ splitting of cadaveric livers. The ultimate expansion of a limited donor pool. Ann Surg 1996; 224:331.
26. Goss JA, Yersiz H, Shackleton CR, et al. In situ splitting of the cadaveric liver for transplantation. Transplantation 1997; 64:871.
27. de Ville de Goyet J, Hausleithner V, Reding R, Lerut J, Janssen M, Otte JB. Impact of innovative techniques on the waiting list and results in pediatric liver transplantation. Transplantation 1993; 56:1130.
28. Gridelli B, Spada M, Petz W, et al. Split-liver transplantation eliminates the need for living-donor liver transplantation in children with end-stage cholestatic liver disease. Transplantation 2003; 75:1197.
29. Renz JF, Emond JC, Yersiz H, Ascher NL, Busuttil RW. Split-liver transplantation in the United States: outcomes of a national survey. Ann Surg 2004; 239:172.
30. Singer PA, Siegler M, Whitington PF, et al. Ethics of liver transplantation with living donors. N Engl J Med 1989; 321:620.
31. Malago M, Rogiers X, Burdelski M, Broelsch CE. Living related liver transplantation: 36 cases at the University of Hamburg. Transplant Proc 1994; 26:3620.
32. Otte JB. Is it right to develop living related liver transplantation? Do reduced and split livers not suffice to cover the needs? Transpl Int 1995; 8:69.
33. Ozawa K, Uemoto S, Tanaka K, et al. An appraisal of pediatric liver transplantation from living relatives. Initial clinical experiences in 20 pediatric liver transplantations from living relatives as donors. Ann Surg 1992:216:547.
34. Strong RW, Lynch SV, Ong TH, Matsunami H, Koido Y, Balderson GA. Successful liver transplantation from a living donor to her son. N Engl J Med 1990; 322:1505.
35. Otte JB. Donor complications and outcomes in live-liver transplantation. Transplantation 2003; 75:1625.
36. Otte JB, Rosati, Janssen M. Parental experience with live-related donor liver transplantation. Pediatr Transplant 2004; 8:317
37. Surman OS. The ethics of partial-liver donation. N Engl J Med 2002; 346:1038.
38. Strong R, Ong TH, Pillay P, Wall D, Balderson G, Lynch S. A new method of segmental orthotopic liver transplantation in children. Surgery 1988; 104:104.
39. Ringe B, Pichlmayr R, Burdelski M. A new technique of hepatic vein reconstruction in partial liver transplantation. Transpl Int 1988; 1:30.
40. Emond JC, Heffron TG, Whitington PF, Broelsch CE. Reconstruction of the hepatic vein in reduced size hepatic transplantation. Surg Gynecol Obstet 1993; 176:11.
41. Tan KC, Yandza T, de Hemptinne B, Clapuyt P, Claus D, Otte JB. Hepatic artery thrombosis in pediatric liver transplantation. J Pediatr Surg 1988; 23:927.
42. Stevens LH, Emond JC, Piper JB, et al. Hepatic artery thrombosis in infants. A comparison of whole livers, reduced-size grafts, and grafts from living-related donors. Transplantation 1992; 53:396.
43. Hatano E, Terajima H, Yabe S, et al. Hepatic artery thrombosis in living related liver transplantation. Transplantation 1997; 64:1443.
44. Chardot C, Herrera JM, Debray D, et al. Portal vein complications after liver transplantation for biliary atresia. Liver Transpl Surg 1997; 3:351.
45. de Ville de Goyet J, Gibbs P, Clapuyt P, Reding R, Sokal EM, Otte JB. Original extrahilar approach for hepatic portal revascularization and relief of extrahepatic portal hypertension related to later portal vein thrombosis after pediatric liver transplantation. Long term results. Transplantation 1996; 62:71.
46. Egawa H, Inomata Y, Uemoto S, et al. Biliary anastomotic complications in 400 living related liver transplantations. World J Surg 2001; 25:1300.
47. Sanchez-Urdazpal L, Gores GJ, Ward EM, et al. Ischemic-type biliary complications after orthotopic liver transplantation. Hepatology 1992;,16:49.
48. Schwarzenberg SJ, Sharp HL, Payne WD, et al. Biliary stricture in living-related donor liver transplantation: management with balloon dilation. Pediatr Transplant 2002; 6:132.
49. Goulet OJ, de Ville de Goyet J, Otte JB, Ricour C. Preoperative nutritional evaluation and support for liver transplantation in children. Transplant Proc 1987; 19:3249.
50. Sokal E. Les acides aminés branchés dans l'alimentation des cholestases néonatales et leur inclusion dans une diète prête à l'emploi destinée à l'alimentation des cholestases néonatales et infantiles. Mini Acta Soc Belg Pediatr 1996; 28:38.
51. Sokal EM, Van Hoorebeeck N, Van Obbergh L, Otte JB, Buts JP. Upper gastro-intestinal tract bleeding in cirrhotic children candidates for liver transplantation. Eur J Pediatr 1992; 151:326.
52. Otte JB, de Ville de Goyet J, Reding R et al. Sequential treatment of biliary atresia with Kasaiportoenterostomy and liver transplantation: a review. Hepatology 1994; 20:41S.
53. Kasai M, Kimura S, Asakura Y. Surgical treatment of biliary atresia. J Pediatr Surg 1968; 3:665.

54. Van Obbergh L, Carlier M, DeClety SC, et al. Liver transplantation and pulmonary gas exchanges in hypoxemic children. Am Rev Respir Dis 1993; 148:1408.
55. Van Obbergh LJ, Carlier M, DeKock M, Otte JB, Moulin D, Veyckemans F. Hepatopulmonary syndrome and liver transplantation: a review of the peroperative management of seven paediatric cases. Paediatr Anaesth 1998; 59.
56. Hadzic N, Davenport M, Tizzard S, Singer J, Howard ER, Mieli-Vergani G. Long-term survival following Kasaiportoenterostomy: is chronic liver disease inevitable? J Pediatr Gastroenterol Nutr 2003; 37:430.
57. Kurbegov AC, Setchell KD, Haas JE, et al. Biliary diversion for progressive familial intrahepatic cholestasis: improved liver morphology and bile acid profile. Gastroenterology 2003; 1227.
58. Melter M, Rodeck B, Kardorff R, et al. Progressive familial intrahepatic cholestasis: partial biliary diversion normalizes serum lipids and improves growth in noncirrhotic patients. Am J Gastroenterol 2000; 5:3522.
59. Ovaert C, Germeau C, Barrea C, et al. Elevated right ventricular pressures are not a contraindication to liver transplantation in Alagille syndrome. Transplantation 2001; 72:345.
60. Sokal EM, Silva ES, Hermans D, et al. Orthotopic liver transplantation for Crigler–Najjar type I disease in six children. Transplantation 1995; 60:1095.
61. Cochat P, Gaulier JM, Koch Nogueira PC, et al. Combined liver-kidney transplantation in primary hyperoxaluria type 1. Eur J Pediatr 1999; 58[Suppl 2]:S75.
62. Sutcliffe RP, Maguire DD, Muiesan P, et al. Liver transplantation for Wilson's disease: long-term results and quality-of-life assessment. Transplantation 2003; 75:1003.
63. Holme E, Lindstedt S. Nontransplant treatment of tyrosinemia. Clin Liver Dis 2000; 805.
64. Crone J, Moslinger D, Bodamer OA, et al. Reversibility of cirrhotic regenerative liver nodules upon NTBC treatment in a child with tyrosinaemia type I. Acta Paediatr 2003; 625.
65. Sokal EM, Ulla L, Harvengt C, Otte JB. Liver transplantation for familial hypercholesterolemia before the onset of cardiovascular complications. Transplantation 1993; 56:432.
66. Fridell JA, Bond GJ, Mazariegos GV, et al. Liver transplantation in children with cystic fibrosis: a long-term longitudinal review of a single center's experience. J Pediatr Surg 2003; 38:1152.
67. Sokal EM, Sokol R, Cormier V, et al. Liver transplantation in mitochondrial respiratory chain disorders. Eur J Pediatr 1999; 58[Suppl 2]:S81.
68. Faivre L, Houssin D, Valayer J, Brouard J, Hadchouel M, Bernard O. Long-term outcome of liver transplantation in patients with glycogen storage disease type Ia. J Inherit Metab Dis 1999; 723.
69. Lerut JP, Ciccarelli O, Sempoux C, et al. Glycogenosis storage type I diseases and evolutive adenomatosis: an indication for liver transplantation. Transpl Int 2003; 16:879.
70. Sokal EM, Van Hoof F, Alberti D, de Villede Goyet J, de Barsy T, Otte JB. Progressive cardiac failure following orthotopic liver transplantation for type IV glycogenosis. Eur J Pediatr 1992; 51:200.
71. Rosenthal P, Podesta L, Grier R, et al. Failure of liver transplantation to diminish cardiac deposits of amylopectin and leukocyte inclusions in type IV glycogen storage disease. Liver Transpl Surg 1995; 1:373.
72. Selby R, Starzl TE, Yunis E, Brown BI, Kendall RS, Tzakis A. Liver transplantation for type IV glycogen storage disease. N Engl J Med 1991; 324:39.
73. Starzl TE, Demetris AJ, Trucco M, et al. Chimerism after liver transplantation for type IV glycogen storage disease and type 1 Gaucher's disease. N Engl J Med 1993; 328:745.
74. Devictor D, Desplanques L, Debray D, et al. Emergency liver transplantation for fulminant liver failure in infants and children. Hepatology 1992; 16:1156.
75. Pritchard J, Brown J, Shafford E, et al. Cisplatin, doxorubicin, and delayed surgery for childhood hepatoblastoma: a successful approach—results of the first prospective study of the International Society of Pediatric Oncology. J Clin Oncol 2000; 3819.
76. Schnater JM, Aronson DC, Plaschkes J, et al. Surgical view of the treatment of patients with hepatoblastoma: results from the first prospective trial of the International Society of Pediatric Oncology Liver Tumor Study Group. Cancer 2002; 40:1111.
77. Otte JB, Pritchard J, Aronson DC, et al. Liver transplantation for hepatoblastoma: results from the International Society of Pediatric Oncology (SIOP) study. SIOPEL-1 and review of the world experience. Pediatr Blood Cancer 2004; 42:74.
78. Petz W, Spada M, Sonzogni A, et al. Pediatric split liver transplantation using elderly donors. Transplant Proc 2001; 33 1361.
79. McDiarmid SV, Davies DB, Edwards EB. Improved graft survival of pediatric liver recipients transplanted with pediatric-aged liver donors. Transplantation 2000; 70:1283.
80. Sieders E, Peeters PM, TenVergert EM, et al. Graft loss after pediatric liver transplantation. Ann Surg 2002; 235:125.
81. Roberts JP, Hulbert-Shearon TE, Merion RM, Wolfe RA, Port FK. Influence of graft type on outcomes after pediatric liver transplantation. Am J Transplant 2004; 4:373.
82. Reding R, Tri T, Bourdeaux C, et al. Pediatric liver transplantation (LT) with living-related donors (LRD) provides significantly better graft survival than LT with post-mortem donors (PMD): a comparative study in 236 children (abstract). Am J Transplant 2003; 3 [Suppl 5]:306.
83. Emond JC. Living donor liver transplantation in children: what to recommend? Am J Transplant 2004; 4:293.
84. Diem HV, Evrard V, Vinh HT, et al. Pediatric liver transplantation for biliary atresia: results of primary grafts in 328 recipients. Transplantation 2003; 75:1692.
85. Chardot C, Carton M, Spire-Bendelac N, Le Pommelet C, Golmard JL, Auvert B. Prognosis of biliary atresia in the era of liver transplantation: French national study from 1986 to 1996. Hepatology 1999; 30:606.
86. Prachalias AA, Kalife M, Francavilla R, et al. Liver transplantation for alpha-1-antitrypsin deficiency in children. Transpl Int 2000; 13:207.
87. Sokal EM, Antunes H, Beguin C, et al. Early signs and risk factors for the increased incidence of Epstein–Barr virus-related posttransplant lymphoproliferative diseases in pediatric liver transplant recipients treated with tacrolimus. Transplantation 1997; 64:1438.
88. Sokal EM, Caragiozoglou T, Lamy M, Reding R, Otte JB. Epstein–Barr virus serology and Epstein–Barr virus-associated lymphoproliferative disorders in pediatric liver transplant recipients. Transplantation 1993; 56:1394.
89. Smets F, Bodeus M, Goubau P, et al. Characteristics of Epstein–Barr virus primary infection in pediatric liver transplant recipients. J Hepatol 2000; 32:100.
90. Smets F, Latinne D, Bazin H, et al. Ratio between Epstein–Barr viral load and anti-Epstein–Barr virus specific T-cell response as a predictive marker of posttransplantlymphoproliferative disease. Transplantation 2002; 73:1603.

91. Kelly DA, Jara P, Rodeck P, et al. Tacrolimus and steroids versus ciclosporinmicroemulsion, steroids and azathioprine in children undergoing liver transplantation: randomized European multicenter trial. Lancet 2004; 364:1054.
92. Reding R. [Transplantation surgery and immunology: from origins to new paradigms of immune tolerance] Chirurgie et immunologiede transplantation: des originesaux nouveaux paradigmesde la tolerance. Bull Mem Acad R Med Belg 2002; 157:439.
93. Kelly DA, Goddard S. Is there any immunological advantage to living-related donor liver transplantation in pediatric recipients? Pediatr Transplant 2002; 6:364.
94. Toyoki Y, Renz JF, Mudge C, Ascher NL, Roberts JP, Rosenthal P. Allograft rejection in pediatric liver transplantation: comparison between cadaveric and living related donors. Pediatr Transplant 2002; 6:301.
95. Katz SM, Ozaki CF, Monsour HP Jr, et al. Pediatric living-related and cadaveric liver transplantation: a single center experience. Transplant Proc 1994; 26:145.
96. Alonso EM, Piper JB, Echols G, Thistlethwaite JR, WhitingtonPF. Allograft rejection in pediatric recipients of living related liver transplants. Hepatology 1996; 23:40.
97. Reding R, de Ville de Goyet J, Delbeke I, et al. Pediatric liver transplantation with cadaveric or living related donors: comparative results in 90 elective recipients of primary grafts. J Pediatr 1999; 134:280.
98. Gupta P, Hart J, Cronin D, Kelly S, Millis JM, Brady L. Risk factors for chronic rejection after pediatric liver transplantation. Transplantation 2001; 72:1098.
99. Kerkar N, Hadzic N, Davies ET, et al. De-novo autoimmune hepatitis after liver transplantation. Lancet 1998; 351:409.
100. Andries S, Casamayou L, Sempoux C, et al. Posttransplant immune hepatitis in pediatric liver transplant recipients: incidence and maintenance therapy with azathioprine. Transplantation 2001; 72:267.
101. Mazariegos GV, Reyes J, Marino IR, et al. Weaning of immunosuppression in liver transplant recipients Transplantation 1997; 63:243.
102. Fine RN, Alonso EM, Fischel JE, Bucuvalas JC, Enos RA, Gore-Langton RE. Pediatric transplantation of the kidney, liver and heart: summary report. Pediatr Transplant 2004; 8:75.
103. Maes M, Sokal E, Otte JB. Growth factors in children with end-stage liver disease before and after liver transplantation: a review. Pediatr Transplant 1997; 1:171.
104. Renz JF, de Roos M, Rosenthal P, et al. Posttransplantation growth in pediatric liver recipients. Liver Transpl 2001; 7:1040.
105. Lykavieris P, van Mil S, Cresteil D, et al. Progressive familial intrahepatic cholestasis type 1 and extrahepatic features: no catch-up of stature growth, exacerbation of diarrhea, and appearance of liver steatosis after liver transplantation. J Hepatol 2003; 39:447.
106. Codoner-Franch P, Bernard O, Alvarez F. Long-term follow-up of growth in height after successful liver transplantation. J Pediatr 1994; 124: 368.
107. Fine RN, Otte JB, Tejani A. Corticosteroid elimination in pediatric solid organ transplantation. Pediatr Transplant 1998; 2:3.
108. Reding R. Steroid withdrawal in liver transplantation: benefits, risks, and unanswered questions. Transplantation 2000; 70:405.
109. Reding R, Gras J, Sokal E, Otte JB, Davies HF. Steroid-free liver transplantation in children. Lancet 2003; 362:2068.
110. Sarna S, Sipila I, Ronnholm K, Koistinen R, Holmberg C. Recombinant human growth hormone improves growth in children receiving glucocorticoid treatment after liver transplantation. J Clin Endocrinol Metab 1996; 81:1476.
111. KennardBD, Stewart SM, Phelan-McAuliffe D, et al. Academic outcome in long-term survivors of pediatric liver transplantation. J Dev Behav Pediatr 1999; 20:17.
112. Tornqvist J, Van Broeck N, Finkenauer C, et al. Long-term psychosocial adjustment following pediatric liver transplantation. Pediatr Transplant 1999; 3:115.
113. van Mourik ID, Beath SV, Brook GA, et al. Long-term nutritional and neurodevelopmental outcome of liver transplantation in infants aged less than 12 months. J Pediatr Gastroenterol Nutr 2000; 30:269.
114. Gritti A, DiSarno AM, Comito M, DeVincenzo A, DePaola P, Vajro P. Psychological impact of liver transplantation on children's inner worlds. Pediatr Transplant 2001; 5:37.
115. Schwering KL, Febo-Mandl F, Finkenauer C, Rime B, Hayez JY, Otte JB. Psychological and social adjustment after pediatric liver transplantation as a function of age at surgery and of time elapsed since transplantation. Pediatr Transplant 1997; 1:138.
116. Schulz KH, Hofmann C, Sander K, et al. [Living organ donation vs. cadaveric donation—study of liver transplanted children and their families] Lebendspende vs. Fremdspende—einekatamnestische Studielebertransplantierter Kinderundihrer Familien. Psychother Psychosom Med Psychol 2001; 51:452.
117. Haufroid V, Mourad M, Van Kerckove V, et al. The effect of CYP3A5 and MDR1(ABCB1) polymorphins on cyclosporine and tacrolimus dose requirements and trough blood levels in stable renal transplant patients. Pharmacogenetics 2004; 14:147.
118. Thummel K. A genetic test for immunosuppressant dose selection? Pharmacogenetics 2004; 14:145.
119. Hebert MF, Dowling AL, Gierwatowski C, et al. Association between ABCB1 (multidrug resistance transporter) genotype and post-liver transplantation renal dysfunction in patients receiving calcineurin inhibitors. Pharmacogenetics 2003; 13:661.
120. Diem HV, Sokal EM, Janssen M, Otte JB, Reding R. Steroid withdrawal after pediatric liver transplantation: a long-term follow-up study in 109 recipients. Transplantation 2003; 75:1664.
121. Mazariegos GV, Reyes J, Webber SA, et al. Cytokine gene polymorphisms in children successfully withdrawn from immunosuppression after liver transplantation. Transplantation 2002; 73:1342.
122. Takatsuki M, Uemoto S, Inomata Y, et al. Weaning of immunosuppression in living donor liver transplant recipients. Transplantation 2001; 72:449.
123. Starzl TE, Murase N, Abu-Elmagd K, et al. Tolerogenic immunosuppression for organ transplantation. Lancet 2003; 361:1502.
124. Sokal EM, Smets F, Bourgois A, et al. Hepatocyte transplantation in a 4-year-old girl with peroxisomal biogenesis disease: technique, safety, and metabolic follow-up. Transplantation 2003; 76:735.
125. Allen KJ, Soriano HE. Liver cell transplantation: the road to clinical application. J Lab Clin Med 2001; 138:298.