Pediatric Liver Transplantation

29

Denis Devictor and Pierre Tissieres

Abstract

Pediatric Liver Transplantation (LT) is one of the most successful solid organ transplants with long term survival more than 80 %. Nowadays, pediatric liver transplantations in children are routinely performed in all developed countries across the world and the acquired experience is considerable. This success is dependent on constant collaboration between pediatricians, hepatologists, surgeons, intensivists, nurses, transplant coordinators, dieticians, psychologists and social workers. Many aspects have contributed to improve survival in children post-LT, especially advancements in pre-, peri-, and post- transplant management. The development of new surgical techniques, such as reduction hepatectomy, split-LT and the introduction of living related LT, has extended LT to infants under the age of 1 year and even in neonates. Progress in the last 20 years has also been characterized in large part by the introduction of calcineurin inhibitors, cyclosporine and tacrolimus that today represent the keystone of most immunosuppressive protocols. One major problem remains the lack of donors. Donation after cardiac death offers a new possibility to increase the pool of potential donors. In children with acute liver failure, increasing interest has centered on the possibility of providing temporary liver support based on extracorporeal devices (artificial and bioartificial) or on hepatocyte transplantation, either as a bridge to liver transplantation or ideally to obviate the need for it. Similarly, hepatocyte transplantation offers new perspective in infants and children with metabolic failure. As long-term survival increases, attention has now focused on the quality of life achieved by children undergoing transplantation.

Keywords

Liver transplantation • Liver graft • Children • Neonates • Biliary atresia • Cholestatic diseases • Acute liver failure • Metabolic diseases • Immunosuppression • Surgery • Results • Outcome

Introduction

Pediatric liver transplantation (LT) is one of the most successful solid organ transplants [1–3]. It has become a well-established and successful strategy in treating children with end-stage liver disease as well as children with irreversible acute liver failure, with excellent success and limited mortality. In most centers, the 1-year actuarial survival rate is higher than 90 % in elective patients and higher than 70 % in children with acute liver failure [4]. Long-term survival is also excellent – more than 80 % of children will survive to become teenagers and adults with

D. Devictor, MD, PhD (✉) • P. Tissieres, MD, PhD
Department of Pediatrics, Hôpitaux Universitaires Paris Sud,
Hôpital de Bicêtre. University Paris 11-Sud,
78 rue du Général LECLERC, 94275 Le Kremlin-Bicêtre, France
e-mail: denis.devictor@bct.aphp.fr; pierre.tissieres@bct.aphp.fr

D.S. Wheeler et al. (eds.), *Pediatric Critical Care Medicine*,
DOI 10.1007/978-1-4471-6359-6_29, © Springer-Verlag London 2014

Table 29.1 Indications for liver transplantation in children and outcomes

	Frequency (%)	
	SPLIT registry[a]	BICETRE
Diagnosis	1995–2002	1986–2002
Number of patients	n = 1092	n = 568
Number of transplantations	NA	648
Cholestatic liver disease	66 %	77 %
Biliary atresia	42 %	53 %
Others	14 %	34 %
Alagille syndrome		6 %
Sclerosing cholangitis,		3.5 %
Progressive familial intrahepatic cholestasis		8 %
Alpha-1-antitrypsine deficiency		4.5 %
Acute liver failure	13 %	11 %
Metabolic diseases	12 %	9 %
Others	13 %	3 %
Liver graft survival	75 %[b]	65 %[c]
Patient survival	69 %[b]	83 %[c]

SPLIT Studies of pediatric liver transplantation, *NA* not available
[a]Data from Ref. [3]
[b]15-year outcome
[c]3-year outcome

excellent health-related quality of life [5–7]. Many aspects have contributed to improved survival in children post-LT, especially advancements in pre-, peri-, and post- transplant management [8]. The development of new surgical techniques, such as reduction hepatectomy, split-LT and the introduction of living related LT, has extended LT to infants under the age of 1 year and weighing less than 8 kg, which has effectively reduced the waiting list mortality from 25 to 5 %. Nowadays LT in children are routinely performed in all developed countries across the world and the acquired experience is considerable. Reports of experience from single centers provide are certainly encouraging, and the databases of the Studies in Pediatric Liver Transplantation (SPLIT group) and of the pediatric acute liver failure study group (PALF group) are also invaluable sources demonstrating these marked improvements in outcome [5, 9–11]. For instance, the data of the SPLIT group allows analysis of currently more than 4,000 North-American children who have undergone LT [12–15]. Similarly, the PALF group provides considerable data to improve our understanding on the treatment and outcome of children with acute liver failure and to identify factors to predict need for LT in children with ALF [10].

Indications for Liver Transplantation

The main indications for LT in the pediatric population can be broadly separated in four groups: cholestatic liver diseases, acute liver failure, metabolic liver disease, and liver tumors (Tables 29.1 and 29.2) [1, 16].

Table 29.2 Patient characteristics of 2,982 children who underwent a first liver transplantation registered in SPLIT from 1995 to 2008

	Total N = 2982	
	N	%
Age at transplant		
Missing	1	0.0
0–6 month	260	8.7
6–12 month	725	24.3
1–5 year	962	32.3
5–13 year	616	20.7
13 + year	418	14.0
Race		
Missing	47	1.6
White	1668	56.3
Black	464	15.6
Hispanic	494	16.6
Other	299	10.0
Sex		
Missing	1	0.0
Male	1407	47.2
Female	1574	52.8
Primary disease		
Biliary atresia	1203	40.3
Other cholestatic or metabolic	837	28.1
Fulminant liver failure	420	14.1
Cirrhosis	1996	6.6
Other	326	10.9
Patient status at transplant		
Missing	15	0.5
ICU/intubated	369	12.4
ICU/non intubated	407	13.6
Hospitalized	514	17.2
Home	1677	56.2

Based on data from Ref. [10]

Cholestatic Liver Disease

Biliary atresia is the most common cause of chronic cholestasis in infants and accounts for nearly 50 % of the indications for LT in children. Most of these small children have undergone a Kasai procedure that failed to re-establish effective biliary flow. Consequently, they develop secondary biliary cirrhosis leading to chronic end-stage liver failure. Out of 1187 children transplanted in North America between 1995 and May 2002, 33.5 % were ≤ 12 months old at the time of transplantation, 55.6 % had cholestatic disease, and 41.6 % had biliary atresia. Of the children transplanted at < 1 year of age, 65.6 % had biliary atresia [17]. Indications for LT in children with biliary atresia are cholangitis or progressive jaundice (35 %), portal hypertension or hepatorenal syndrome (41 %), and decreased liver synthetic functions. Intrahepatic cholestasis such as sclerosing cholangitis, Alagille's syndrome, non-syndromic paucity of intrahepatic bile ducts, and progressive familial intrahepatic cholestasis represent approximately 15 % of all transplantations [11].

Table 29.3 Causes of ALF in infants and children admitted at the Bicêtre Hospital PICU (1986–2007) and compared to those reported by the PALF[a] study group

Causes		Infants <1 year (n = 107)	Children ≥1 year (n = 128)	Total (n = 235)	Infants <7 month (n = 149)	≥ 1 year ≥7 month (n = 554)	Total (n = 703)
Infectious	HAV, HBV, herpes simplex, HHV6, EBV, enterovirus, adenovirus, parvovirus B19, dengue fever	19 (18 %)	33 (26 %)	52 (22 %)	20 (13 %)	25 (4 %)	45 (6 %)
Undetermined		10 (9 %)	32 (25 %)	42 (18 %)	61 (49 %)	268(48 %)	329 (47 %)
Toxic	Acetaminophen, sulfamide, sodium valproate, sulfasalazine, halothane, amanita phalloides, chemotherapy	7 (7 %)	25 (19 %)	32 (14 %)	3 (2 %)	108 (19 %)	111 (16 %)
Autoimmune	Giant cell hepatitis, LKM or LC1 autoimmune hepatitis	8 (7 %)	7 (5 %)	15 (6 %)	0 (0 %)	48 (9 %)	48 (7 %)
Hematologic	Familial lymphohistiocytosis, macrophage activation syndrome, leukemia	7 (7 %)	3 (2 %)	10 (4 %)	–	–	–
Vascular	Veno-occlusive disease, Budd Chiari syndrome	2 (2 %)	1 (1 %)	3 (1 %)	–	–	–
Other	Ischemic liver	–	–	–	38 (25 %)	64 (12 %)	102 (14 %)

Based on data from Ref. [24]
HAV hepatitis A virus, *HBV* hepatitis B virus, *HHV* human herpes virus, *EBV* Epstein-Barr virus, *LKM* liver kidney microsome, *LC1* liver cytosol 1
[a]PALF: Pediatric Acute Liver failure study group adapted from Refs. [11, 12]

Metabolic Diseases

Metabolic diseases are the second most common indication for LT [18–22]. They include primary hepatic diseases such as Wilson disease, alpha-1-antitrypsin deficiency, and cystic fibrosis, as well as primarily nonhepatic diseases such as ornithine transcarbamylase deficiency, Criggler-Najjar syndrome type 1, primary hyperoxaliuria type 1, and organic academia. In children with primary hyperoxaluria type I, combined liver and kidney transplantation should be considered when irreversible renal injury from oxalic acid accumulation has developed. Liver transplantation has been recently suggested for the treatment of organic acidemia (propionic aciduria, methylmalonic aciduria) as well. However, LT does not correct the enzyme deficiency in other organs except the liver, and patients remain at risk of severe extra-hepatic complications. Children transplanted for metabolic diseases generally have excellent outcomes [18, 20, 21].

Acute Liver Failure

Acute liver failure (ALF) accounts for approximately 10 % of all LTs in children [23–26]. The causes of acute liver failure are age-dependent (Table 29.3). For example, in neonates and infants the main causes are viral infections and inborn metabolic disorders, whereas in children the main causes are drug-induced acute liver failure, autoimmune hepatitis and viral infections [10, 23, 24, 27]. However, in around 50 % of the cases, the cause of acute liver failure cannot be determined. This high proportion of undetermined acute liver failure can be explained because a significant number of these cases have undergone an incomplete screening, especially regarding metabolic diseases and autoimmune liver disease [24, 25]. Graft survival in children with acute liver failure is significantly lower than that of children transplanted for other causes [24, 28]. Grade 4 encephalopathy, age < 1 year, and dialysis before transplantation are risk factors for poor outcome [29]. In children with acute liver failure, increasing interest has centered on the possibility of providing temporary liver support with extracorporeal devices (artificial and bioartificial) or with hepatocyte transplantation, either as a bridge to liver transplantation or ideally to obviate the need for it [30].

Other Indications

Liver tumors are mainly represented by hepatoblastoma. Children with hepatoblastoma should first be treated with chemotherapy and then evaluated for resection or transplantation [31, 32]. Hepatocellular carcinoma in children is rare and is often secondary to another chronic underlying disease liver disease. The development of hepatocellular carcinoma has been reported in greater frequency in children with biliary atresia, Alagille's syndrome, progressive intrahepatic cholestasis, and tyrosinemia. In children with tyrosinemia, there was a 33 % incidence of hepatocellular

carcinoma before 2 years of age that seems to be reduced if not eliminated by 2-(2-nitro-4-3 trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) therapy [16].

Contraindications to Liver Transplantation

The list of contraindications to LT in children has been shortened considerably because surgical techniques and medical management have improved significantly over time [1]. Absolute contraindications to pediatric LT are conditions in which LT is futile therapy: (1) unresectable extrahepatic malignant tumor considered incurable by standard oncologic criteria; (2) concomitant end-stage organ failure that cannot be corrected by a combined transplant; (3) uncontrolled systemic infection or multiple organ failure, and (4) irreversible serious neurological damage. Relative contraindications include malignancy that is considered cured or curable by standard oncologic criteria and treatable infection. Obviously the contraindications should be discussed on a case-by-case analysis.

Evaluation of Potential LT Recipients

The appropriate selection and evaluation of potential LT recipients is crucial to achieving good outcomes [1, 16]. The primary goal of the evaluation process is to identify appropriate candidates for LT. The first step is to determine whether LT remains the best option and that no other medical therapies could be life sustaining with adequate quality of life. Contraindications should be identified at this stage of the evaluation process. Once the indication is confirmed, the second step is to determine the severity of the disease and assess for any complications or co-morbidities.

In the ideal situation, LT would be offered before the onset of life-threatening complications. To determine the degree of severity of liver disease, the medical screening requires specific blood tests, radiologic evaluation, and consultations with specialists. The major functions of the liver can be grouped into four general categories: (1) protein synthesis, (2) bile formation and excretion, (3) immunologic functions, (4) and hemodynamic functions. All these functions are assessed with appropriate laboratory and radiologic exams. The laboratory tests include exposures to viral infections (cytomegalovirus, Epstein-Barr virus in particular). Radiologic evaluation should identify vascular anomalies or portal vein thrombosis. Radiologic evaluation includes a Doppler ultrasound and may also require magnetic resonance imaging or computed tomography angiography. Assessment for extrahepatic disease that might impact on peri-, per-, or operative management is an important part of the evaluation, and will vary with the underlying disease. Children with Alagille syndrome for instance, require careful cardiac and renal assessment, since these organs are involved in this syndrome.

The second goal of this evaluation is to establish a pre-transplant program. The importance of nutritional support at every stage of the management of liver disease should be stressed, since growth impairment has been associated with longer post-transplant hospital stays [33]. The pre-transplant therapeutic plan also includes immunizations, prevention or treatment of drug-induced side effects, education and support to the patient and family (especially to inform and educate both the parents and the child if possible, on LT procedure and on the post-operative period), and evaluate social status and logistic issues. Preparation of the recipient and family for LT is a key issue requiring the constant collaboration between the primary care practitioner, pediatricians, hepatologists, surgeons, nurses, transplant coordinators, dieticians, psychologists and social workers. The collaboration with the primary care practitioner is crucial particularly to optimize the communication between the patient and family with the transplant team, to complete and often accelerate immunization schedules before transplantation, and to optimize nutritional support and detect potential complications [1].

Prioritization

In most countries with an established organ transplantation network, graft allocation is based on the concept that organs need to be allocated to the sickest patients. Most systems preferentially allocate pediatric donors to pediatric recipients. However, the policy to allocate organs is undergoing constant adaptations and modifications because of a persistent donor shortage. In the United States, the PELD score was introduced in 2002 to stratify the degree of illness in children with similar diseases who are competing for pediatric liver grafts. This score is calculated from a formula based on objective medical criteria including total bilirubin (mg/dL), INR, serum albumin (g/dL), age less than 1 year, and growth failure (height less than 2 standard deviations from the mean for age and gender) [1, 16, 34–36]. Additional PELD points are awarded for specific risk factors not taken into account in the PELD score, such as hepatopulmonary syndrome, metabolic diseases, and liver tumors. The adoption of the PELD score in the USA has improved the access and accountability of the allocation system. Since the use of the PELD score, fewer children are now dying on the waiting list [1, 35]. However, the PELD score does not cover all pediatric situations [1]. It is currently used only for children up to 12 years old, does not take into account potential complications of end-stage liver disease (hepatopulmonary syndrome for instance), and is not adapted to children with acute liver failure, liver tumors or metabolic diseases.

The Transplant Operation

It is not possible to review all the surgical aspect of LT, however it is important for pediatric intensivists to have a basic understanding of the processes involved in harvesting the organ from the donor and transplanting it to the recipient. The technical aspects of the arterial reconstruction, the portal vein anastomosis, and the restoration of biliary tract continuity are important to consider for the pediatric intensivist as each procedure has its own share of complications. Therefore the communication between the surgeons, radiologists and intensivist is crucial during the peri and post-operative period.

Allograft Procurement

Donor Selection

Selection of an appropriate liver donor is vitally important to the short and long-term success of the transplantation. Particular attention is paid to donor age, cause of brain death, intensive care hospitalization time, infections, and presence of hemodynamic stability. No consistent data exist on the effect of donor age on the long-term results of pediatric LT. Up to the early 1980s, the only technical option was to transplant the whole liver of a donor with a weight as close as possible to that of the recipient. However, the shortage of pediatric cadaveric donors has resulted in a high mortality rate on the waiting list. The development of techniques that allow surgeons to transplant portion of livers from adult donors has expanded the donor pool and has been a major advancement in reducing the waiting period and improving the survival rates of pediatric LT. Currently reduced-liver grafts to the left lateral segments and split livers provide the majority of grafts in infants, whereas left or right lobes are used in older recipients (Table 29.4).

Table 29.4 Transplant characteristics of 2,982 children who underwent a first liver transplantation registered in SPLIT from 1995 to 2008

	Total N = 2982	
	N	%
Donor organ		
Missing	100	3.4
Live	461	15.5
Whole	1564	52.4
Reduced	482	16.2
Split	375	12.6
Transplant year		
1995–2001	1161	38.9
2002–2008	1821	61.1
Primary immunosuppression		
Missing	128	4.3
Ciclosporine	444	14.9
Tacrolimus	2326	78.0
Other	84	2.8
Donor age		
Missing	213	7.1
0–6 month	148	5.0
6–12 month	121	4.1
1–18 year	1482	49.7
18–50 year	932	31.3
≥ 50 year	86	2.9

Based on data from Ref. [10]

Whole-Liver Transplantation

To date, whole-organ transplantation is used when a cadaveric donor has an approximate recipient size. When using whole-organ grafts, the donor weight should range 15 % above or below that of recipient. Occasionally, abdominal-wall closure may be difficult because of the large size of the liver graft. The subsequent risk is the development of an abdominal compartment syndrome. This may be remedied by the use of a silastic prosthesis on the abdominal wall so that a temporary closure can be made.

Reduced-Size Liver Transplantation

This procedure consists in the procurement of the whole liver from an adult cadaver donor, which is reduced in its size. According to the original description, a right hepatectomy is performed and the left lobe (segments I to IV) is transplanted in a child. This technique allows surgeons to overcome differences in size between the donor and the recipient of up to four or five times. More extended reductions of the graft – for example, only keeping the segments 2 and 3 are also possible, allowing transplantation of liver from donors with a body weight up to 12 times the recipient's one. Estimates of donor graft-to-recipient body weight ratio (optimal between 1.5 and 3 % or 150–200 g, for a recipient who weighs 10 kg) appear to be the most accurate predictor of adequate graft volume. Reduced-size liver transplantation shows similar outcomes to whole-liver transplantation [3, 12, 15, 37, 38]. However, this procedure reduces the pool of liver for adults. Therefore, other option such as split liver and living-related liver transplantation have been developed.

Split-Liver Transplantation

Split-liver transplantation allows two functional allografts. The left lateral segment (segment 2 and 3) is transplanted in a child, whereas the right liver is transplanted into an adult. This procedure increases the ischemia time, with an increased risk of primary dysfunction and technical complications. Because split-liver transplantation may require a prolonged ischemic period, selection of donor patients is crucial [16]. However, the possibility to split the liver in situ can reduce the ischemia time. This procedure has shown comparable results to those obtained with conventional techniques.

Living-Related Liver Transplantation

Living-related liver transplantation accounts for a substantial number of pediatric LT performed in many centers across the world and the only possibility for LT in countries where cadaveric organ procurement was not allowed [39]. The procedure consists in a left lobectomy during which segments 2 and 3 are separated from the remaining liver. Living-related liver transplantation has been widely debated with regard to the ethics of performing major surgery on a healthy person. Donor mortality and morbidity is estimated at approximately 0.2 and 10 % respectively. Evaluation of the donor and the recipient is crucial. Recipient size and age are important, because there is evidence that infants and small children do better than older children with living donor transplantation [40]. In the majority of cases, living related transplants register an excellent outcome for pediatric patients, thanks to the possibility of performing the transplant before the child's clinical condition deteriorates. Living-related liver transplantation should also be considered in children with acute liver failure when no cadaveric grafts are available.

Recipient Procedure

Most liver transplants follow the similar order [16]. The details of the recipient operation cannot be described here. They have been described elsewhere [32]. In brief, LT has three major phases. The first one begins with the recipient hepatectomy. It is often the most difficult part of the procedure because of complicating features (portal hypertension, coagulopathy, and adhesions from prior surgery). The second phase is the anhepatic phase. The graft is placed starting with the vascular outflow anastomosis first, including the hepatic veins and infrahepatic vena cava, followed by the vascular inflow of the portal vein and finally hepatic artery. Following the neo-liver perfusion, the initial blood return to the heart is necessarily cold, acidotic, and hyperkalemic caused by cold perfusion techniques. Significant cardiovascular instability can result in additional hemostatic problems caused by coagulopathy and fibrinolysis. The specialized anesthesia team should be prepared to manage these problems. The biliary anatomosis is performed in the final phase. A Roux-en-Y anastomosis (hepaticojejunostomy) is obviously necessary in patients undergoing LT for biliary atresia. This approach is also used in young children receiving a segmental graft, those with an abnormal native biliary tree, as in sclerosing cholangitis, or if the donor or recipient duct is very small. A direct choledocho-choledochostomy is possible in other patients with a normal native biliary tract.

The operative procedure is marked by important issues, which may influence postoperative management. Severe portal hypertension may result in critical bleeding during removal of the native liver. Bleeding may occur during dissection of extensive adherences, such as in children with biliary atresia who underwent previous portoenterostomy surgeries. Assessment of vascular anastomosis is essential; for example, portal anastomosis in children with biliary atresia may be difficult, as portal vessels are frequently hypoplastic. Arterial anastomosis may preclude important dissection along the infrarenal aorta, with subsequent risk of traumatic lesions to the pancreas. The appearance of the liver graft after unclamping may be informative regarding the quality of the graft. Finally, abdominal closure should be performed in a manner to avoid increased intra-abdominal pressure.

Management During the Early Postoperative Period

After transplantation, children are taken to the PICU for intensive care monitoring and management. Management can be divided into two main issues: the general management of a patient after major abdominal surgery and, specific considerations regarding liver transplantation.

General Post-operative Management

Respiratory

Patients should be weaned from the ventilator and extubated as soon as possible, because prolonged mechanical ventilation has been associated with higher mortality and morbidity. In general, children can be extubated within 1–4 days after transplantation. However, for some children, a more prolonged course of mechanical ventilation is necessary because of increased abdominal pressure, malnutrition, postoperative pain, or other complications such as sepsis, liver dysfunction, refractory ascites, and in rare cases, right phrenic nerve paresis. A daily chest radiograph should be obtained to assess for atelectasis and effusions. Pleural effusions secondary to ascites passing across the diaphragm are common and can be treated with diuretic therapy. In some cases, a pleural pigtail catheter is required. Continuous monitoring of oxygen saturation and expired carbon dioxide, and frequent assessment of arterial blood gas values should also be performed.

Cardiovascular

Continuous arterial pressure and central venous pressure should be monitored. The abdominal catheter drainage should be assessed every hour for extensive bleeding indicating possible hemorrhage from the vascular anastomosis, or coagulopathy, especially in case of primary non-function. Hypotension may be the result of intra-abdominal bleeding, sepsis, or volume depletion. Hypertension may be the results of side effects from immunosuppressive agents, volume overload, or pain.

Gastrointestinal

It is crucial to assess synthetic, metabolic, and excretory function of the graft immediately after transplantation. Absence of intra-abdominal bleeding, and rapid correction of coagulation abnormalities are the best indicators of synthetic function. Adequate metabolic function is reflected in normalizing lactate levels, and if the child is awakening within several hours following the transplant procedure. Clearance of anesthesia is a good indicator of synthetic function. After 48 h, the total bilirubin, coagulations tests, and transaminases are reliable indicators of liver function. Depending upon the degree of graft injury due to ischemia, the transaminases' levels skyrock within 2 days and should be near normal after 7 days.

Renal

Electrolytes and fluid balance should be monitored closely. Massive fluid shifts from ascites, blood loss, and stress from major surgery may occur resulting in hypovolemia, hypotension, metabolic and electrolyte disturbances. With the addition of nephrotoxic drugs, such as tacrolimus and some antibiotics, patients are at higher risk of kidney impairment.

Neurologic

Level of consciousness is an important indicator of graft function. Graft dysfunction is generally indicated by slowness to waken.

Table 29.5 Indications for retransplantation of the liver

Primary non-function	22 %
Chronic allograft rejection	21 %
Hepatic artery thrombosis	18 %
Portal vein thrombosis	17 %
Acute allograft rejection	7 %
Atypical acute allograft rejection	6 %
Biliary complications	3 %
Recurent or de novo viral diseases	5 %
Other	1 %

Based on data from Ref. [41]

Specific Post-operative Considerations

Specific post-operative management of the liver transplant patient includes monitoring for both surgical and medical complications. Surgical complications have reduced over time, but sepsis and rejection remain significant issues (Tables 29.5 and 29.6).

Surgical Considerations

Primary Non-function and Sub-function of the Graft

Primary non-function of the graft is a rare but catastrophic event. It usually occurs within the first 48 h following the procedure, and diagnosis is based on absence of neurologic awakening, hepatic encephalopathy, bleeding, increasing liver enzymes, lactic acidosis, and vasoplegic shock. In cases of split-liver transplant, information regarding the other liver recipient's postoperative course may help in diagnosing primary graft non-function. The only therapy is emergency re-transplantation. Sub-graft function with persistent coagulopathy is also possible but generally reversible within a few days. Although the cause is unknown, it is likely the result of the donor rather than recipient factors and probably related to ischemia/reperfusion injury of the graft, which further emphasizes the critical importance of the donor's selection

Table 29.6 Specific post-operative complications after liver transplantation in children

Ref	Year	Liver transplantation N	HAT	PVC	HV stenosis	Biliary complications	Digestive complications
Bourdeaux et al. [42]	2007						
Total		235	7.6	9.4	1.7	21.7	NA
LRDT		235	1	13	0	30	
Kim et al. [43]	2005						
Total		170	7	1.8	NA	7	3.5
LRDT		51	4	2		6	4
Fouquet et al. [6][a]	2005	280	17	11	NA	20	13
Diamond et al. [12][b]	2007						
Total		2192	7.6	5.5	NA	12	9.8
LRDT		360	6.7	7.5		17.5	11.1
Ueda et al. [44][c]	2006	600	3.3	7.5	3.7	14.5	5.7
Heaton et al. [45][c]	2008	50	6	4	NA	14	

LRDT living related donor transplantation, *HAT* hepatic artery thrombosis, *PVC* portal vein complication (thrombosis or stenosis), *SHV* stenosis, stenosis of the hepatic vein anastomosis

[a]Liver transplantation only for biliary atresia

[b]Complication occurring within the first month after transplantation

[c]Living related liver transplantation only

(cause of cerebral death, hemodynamic stabilities, normoxia, age, etc.), as previously mentioned.

Vascular Complications

Vascular thrombosis is the main postoperative complication that will cause graft loss. Hepatic artery thrombosis occurs in children (5–15 %) three times more frequently than in adults, usually within the first 30 days after transplantation [3, 14]. This complication is directly related to the size of the vessels and thus is most likely in the smallest pediatric recipients and/or small liver grafts [46]. Prevention of hepatic artery thrombosis in these situations is based on anticoagulation, antiplatelet aggregation therapy, and avoiding hemoconcentration. Hepatic artery thrombosis can occur with various clinical presentations, which may include acute allograft failure, biliary obstruction, or sepsis. Suspected hepatic artery thrombosis requires prompt evaluation with duplex sonography, magnetic resonance angiography, or angiogram. Successful thrombectomy is possible if hepatic artery thrombosis diagnosis is made before graft necrosis occurs. Hepatic artery thrombosis can also occur as a late complication and can manifest as biliary strictures, bilomas, or sepsis. These biliary complications are particularly frequent after hepatic artery thrombosis because the hepatic artery offers most of the vascularization to the bile duct. In case of biliary tract necrosis due to hepatic artery thrombosis, the only option is retransplantation.

Early portal vein thrombosis occurs usually within the first week (median, 2 days) after transplantation and requires emergency thrombectomy in most cases. It occurs in 5–10 % of recipients. It is more frequent in children transplanted for biliary atresia, because of pre-existing portal vein hypoplasia. Refractory ascites may indicate a portal thrombosis or stenosis of suprahepatic veins.

Biliary Complications

Bile duct complications (bile leaks, stenosis, strictures) are usually a result of technical problems or of ischemic injury of the donor duct [47, 48]. Early leaks can be diagnosed by the appearance of bile in the drains. Many leaks resolve with decompression by transhepatic tube drainage. Surgical revision of the anastomosis should be performed for those patients with bile peritonitis and those with persistent leaks. As discussed earlier, bile complications resulting from bile duct ischemia secondary to early hepatic artery thrombosis generally require re-transplantation (Table 29.5). Biliary strictures can occur later, even years after transplant, with bile duct dilatation on ultrasound or recurrent cholangitis. They can be definitively diagnosed and treated with percutaneous transhepatic cholangiography with stenting and dilatation, but surgical revision may be necessary in some cases.

Medical Considerations

Infections

Infection is the most common source of morbidity and mortality following transplantation. Because of immunosuppression, patients are at risk of developing nosocomial and opportunistic infections. In addition, the patient's preoperative condition may be a risk factor for sepsis. For example, patients with acute liver failure are known to have defective innate immunity, as characterized by hypocomplementemia and phagocytosis alteration, and children with chronic cholestasis have increased risk for bacterial peritonitis and recurrent cholangitis.

Bacterial sepsis occurs in the immediate post-transplant period and is more frequently due to Gram-negative enteric organisms, *Enterococcus* spp. and *Staphylococcus* spp. Fungal sepsis (*Candida* spp., *Aspergillus* spp.) may occur in the early posttransplant period and hold an elevated mortality if severe infection occurs, making monitoring of colonization index and early treatment mandatory. Frequent postoperative prophylactic regimens include acyclovir, amphotericin B, a β-lactam antibiotic, and trimethoprim-sulfamethoxazole. Although viral and opportunistic infections may occur later after transplantation, Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex and adenovirus can cause early infection that must be recognized. The risk of developing either EBV or CMV infection is influenced by the preoperative serological status of the transplant donor and recipient. Seronegative recipients receiving seropositive donor organs are at greater risk. The development of effective methods of diagnosis, prophylaxis and treatment of CMV with gancyclovir or valgancyclovir means that these diseases are no longer a significant cause of mortality but morbidity remains high. In contrast, the absence of therapy for EBV means that infection rates are high. The development of molecular genetic diagnosis using polymerase chain reaction for EBV means that progressive disease, or post transplant lymphoproloferative disease (PTLD) may be prevented by preemptive reduction of immunosuppression in response to rinsing EBV titers. Various prophylactic protocols have been used to decrease the incidence of symptomatic CMV and EBV infection, although seroconversion in naive recipients inevitably occurs.

Acute Rejection

Despite improved immunosuppressive regimens, acute rejection remains a problem after liver transplantation, and about 20–50 % of patients develop at least one episode of acute rejection in the first weeks after liver transplantation [7, 49]. It can occur later, and is often associated with immunosuppressant noncompliance. The clinical picture includes fever, ascites, and jaundice. Rejection is generally suspected because of increasing liver enzymes and increase in gamma-glutamyltranspeptidase level. Liver biopsy is the key for

diagnosis, and histologic findings of acute rejection are a mixed portal inflammatory infiltrate, predominantly mononuclear cells associated with portal and central vein endothelitis and bile duct damage. The primary treatment is a short course of high-dose methylprednisolone, which is effective in treating rejection in 80 % of cases.

Other Complications and Re-transplantation

Early second look reoperation is commonly used in several centers for the best diagnosis and treatment of bile leakage, hemorrhage, bowel injury, and sepsis for instance. Digestive perforation occurs in 20 % of children with biliary atresia. Acute pancreatitis may occur in <2 % of children who undergo LT but is associated with high mortality. Postoperative cardiopulmonary failure is worth mentioning, as restrictive or obstructive cardiomyopathy (oxalosis, chronic cholestasis) and pulmonary hypertension (hepatopulmonary syndrome, pulmonary vein stenosis in Alagille syndrome) may be encountered.

Re-transplantation is not an uncommon event. Its overall incidence ranges from 10 to 20 % and occurs mainly within the first 30 days following initial transplantation [11, 50]. The majority of re-transplantation results from acute allograft a damage cause by either hepatic artery thrombosis or primary non-function, and acute graft rejection (Table 29.5).

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of diseases, ranging from benign lymphatic hyperplasia to lymphomas. It is favored by the intensity of the immunosuppression and the absence of prior exposure to EBV infection. Treatment of PTLD is based on the clinical aggressiveness of the syndrome and the immunological cell typing. In all cases documented PTLD requires an immediate decrease or withdrawal of immunosuppression. If the tumor expresses the B-cell marker CD20, the anti-CD20 monoclonal antibody rituximab are indicated.

In general recurrence of the primary liver disease in the graft is uncommon in children since liver diseases requiring LT are usually congenital biliary atresia and therefore LT is curative. However, a recurrence is possible if the LT indication is a primary sclerosing cholangitis. De novo autoimmune hepatitis can occur in any graft, regardless of the original disease, and is therefore not considered recurrence of the disease, but a new entity [51, 52]. It may be associated with the use of steroid-free regimes and occur in 2–3 % of children. This form of graft dysfunction is associated with an increasing incidence of non-specific antibodies (ANA, SMA, and rarely LKM), graft hepatitis and elevated immunoglobulins and may be related to the progressive development of graft hepatitis with fibrosis.

Chronic hepatitis has been recently recognized as a prevalent problem in late allografts [1, 53]. Liver biopsy shows a portal inflammation. The treatment of this condition is not clear.

Immunosuppression

The immune system recognizes the liver graft as "non-self" and begins a destructive immune response mediated principally by the T lymphocytes, especially the CD4+ T cell. In addition interleukin -2 (IL-2) activates the secretion of cytotoxic T cells, B cells and macrophages. In order to avoid destruction of the liver graft, immunosuppressive drugs must be administered. The immunosuppressive agents must interrupt the activation of CD4+ T cells and IL-2 production. The incidence of acute and chronic rejection has fallen following the development of newer immunosuppressive drugs, which are more easily absorbed such as cyclosporine microemulsion or more potent such as tarcolimus. The following are the main immunsuppressive drugs used in pediatric LT.

Corticosteroids

Corticosteroids are effective in both the prevention and the treatment of graft rejection. Their mechanisms of action are unclear, but they inhibit IL-2 and reduce the proliferation of T cells (helper and suppressor T cells, cytotoxic T cells), and the migration and activity of neutrophils. However corticosteroids have important side effects. Their use is associated with increased incidence of bacterial, viral and fungal infections, increased risk for developing malignancies, and detrimental metabolic effects in children. The most common metabolic side effects include bone marrow suppression, hypertension, diabetes mellitus, increased appetite, obesity, gastric ulcers, sodium and water retention. Long-term use may result in osteoporosis, growth retardation, avascular necrosis of joints, and depression. For these reasons, most pediatric centers have currently adopted steroid-free immunosuppressive protocols, combining calcineurin inhibitors and antibody to the IL-2 receptors of T cells (basiliximab).

Calcineurin Inhibitors

Progress in liver transplantation in the last 20 years has been characterized in large part by the introduction of calcineurin inhibitors, cyclosporine and tacrolimus, that today represent the keystone of most immunosuppressive protocols. These drugs inhibit T-cell responses and bind to intracellular proteins called immunophilins. This complex binds to and inhibits the phosphatase activity of calcineurin, which block the transcription of cytokines, particularly IL-2. The use of calcineurin inhibitors is associated with side effects, which include nephrotoxicity, neurotoxicity, and hypertension. Most of them are reversible after dose reduction or discontinuation of the drug.

The introduction of cyclosporine in the 1980s was a major advancement because it led to significant increases in patients' and graft survival rates, and a reduction in the incidence and severity of rejection. Administration of cyclosporine usually begins intravenously, during or after LT, with maintenance doses delivered orally. Absorption is dependent upon the presence of bile. Therefore, hepatic dysfunction might limit the absorption of cyclosporine. Microemulsions of cyclosporine are more easily absorbed and allow more stability in the of the desired blood concentration. However, many drugs interact with cyclosporine. Therefore, serum drug levels should be monitored closely. Cyclosporine is also associated with cosmetic side effects such as hypertrichosis and gingival hyperplasia. For all these reasons, over the last 10 years, the use of tacrolimus has increased, and nowadays it is preferred to cyclosporine.

Tacrolimus is 100 times more potent than cyclosporine. Moreover, tacrolimus is associated with less hyperlipidemia and a lower cardiovascular risk than cyclosporine. Comparison between tacrolimus and cyclosporine shows similar 1-year patient and graft survival, as well as steroid-resistant rejection in children treated with tacrolimus. Tacrolimus can be given as a 24-h continuous IV infusion or orally.

Daily determination of calcineurin inhibitors blood level is essential because it will help in dosing immunosuppressive therapy, and in balancing between the risk of infection (in case of over dosage) and rejection (in case of under dosage). Desired concentration of calcineurin inhibitors depends upon the time post – transplant. At 0–3 months post-transplant, cyclosporine and tacrolimus target levels are 200–250 mg/L and 10–15 mg/L, respectively. At 4–12 months post-transplant cyclosporine and tacrolimus levels should be at 150–200 mg/L and 8–10 mg/L, respectively. After 1 year the optimal levels are 50–10 mg/L for cyclosporine and 5–8 mg/l for tacrolimus.

IL-2 Receptor Antibodies

T cells involved in acute rejection act by exposing activation markers such as the IL-2 receptors. Anti IL-2 receptors (basiliximab) combined with anticalcineurin have drastically improved graft survival. Basiliximab is a chimeric (mouse and human) monoclonal antibody. Its safety and tolerability are excellent. As previously mentioned, the combination of these drugs allows steroid-free immunosuppression with no harmful effect on graft acceptance. The patient receives two doses of basiliximab, the first one should be given 6 h after organ reperfusion, and the second on day four after transplantation. This approach reduces hypertension, growth retardation, and the cosmetic effects of steroide therapy.

Other Immunosuppressive Drugs

Mycophenolate mofetil, a selective inhibitor of the inosine monophosphate deshydrogenase, has been successfully used as an alternative immunosuppressive agent in patients with chronic rejection, refractory rejection, or severe calcineurine inhibitor toxicity. Large inter-individual variations indicate the need for therapeutic drug monitoring and individualized dosing.

Sirolimus (rapamycin) is a macrolide antibiotic with immunouppressive properties that acts by blocking T-cell activation by way of IL-2R post receptor signal transduction. It has been used as rescue treatment in chronic rejection and calcineurin inhibitor toxicity.

Results and Outcome

Pediatric LT is one of the most successful solid organ transplants. Although the potential complications are numerous, the overall results of pediatric liver transplantation are excellent, especially for long-term outcome, as most indications for pediatric liver transplantation do not recur within the transplanted allograft, whereas disease recurrence represents a significant cause of long-term graft loss in adults.

Short-Term Results

Survival rates vary according to the age at transplantation and the underlying diagnosis. Survival for children less than 1 year old has improved dramatically [54]. The univariate predictors of graft loss are age less than 6 months, calculated creatinine clearance less than 90, pre-LT hospitalization, pre-LT mechanical ventilation, repeat LT, and infants transplanted for reasons other than cholestatic liver disease [54]. Neonates represent a special population and their outcomes from LT are worthy of consideration [27, 55, 56]. Although small babies have higher complication rates and longer hospital stays following transplantation, neonatal liver transplant recipients now have similar patient and graft survival compared with older children. The underlying diagnosis at transplantation also has an effect on outcomes. Patients with acute liver failure have worse early and long-term survival rates. Although the patient and graft survival are dependent on surgical techniques and patient care, their influence on survival is limited to the initial perioperative period and does not affect long-term outcome. Early postoperative death is mainly related to sepsis, graft failure, multiorgan failure, and cardiopulmonary and neurologic complications, whereas late mortality is mainly related to sepsis. From the SPLIT database, a total of 42 pre-, peri- and post-transplant variables were evaluated in

2982 pediatric recipients of a first LT [9]. Factors affecting patient and graft outcome at 6 months, reoperation for any cause increased the risk for both patient and graft loss by 11 fold and reoperation exclusive of specific complications by fourfold. Vascular thrombosis, bowel perforation, septicemia, and retransplantation, each independently increased the risk of patient and graft loss by three to fourfold. The only baseline factor with similarly high relative risk for patient and graft loss was recipients in the intensive care unit intubated at transplant.

Outcome, Long-Term Complications and Quality of Life

Overall survival of children after liver transplantation is 70–80 % in the largest series, and 15-year graft survival is between 52 and 65 % (Table 29.1). As techniques and patient care improve, actual survival can currently exceed 85 % [4]. Ten years after transplant, 79 % of children attend normal school and in 69 % of them school performance is not delayed [6]. Clinical factors associated with improved post-LT health-related quality of life 20 years after LT are younger age at LT allograft longevity, and strong social support. In a recent study, more than 90 % of pediatric survivors completed high school. After LT, 34 % of pediatric recipients married, and 79 % remained married at 20 years' follow-up [13]. Effective transition strategies from childhood to adulthood are important in adolescents since nonadherence to the treatment is common [57, 58]. One study has reported the psychological adjustment of 116 pediatric LT recipients reaching adulthood. In this study, 76 % considered their quality of life as good or very good. Poor compliance with medications was reported by 45 % of them. Anxiety, loneliness and negative thoughts were expressed by 53, 84, and 47 % of the patients, respectively. Among them, 11 % were being cared for by psychologists or psychiatrists [5].

Despite these encouraging results, late complications are possible. Seventy-three per cent of long-term survivors have abnormal liver histology with centrolobular fibrosis mainly due to chronic rejection [6]. Resistant linear growth impairment is also common in pediatric liver transplant population [59]. Renal dysfunction has also been noted in more than 30 % of long-term survivors [60]. This has modified immunosuppressive practices in at-risk transplant recipients. However current immunosuppressive agents are also associated with an increased risk for diabetes, dyslipidemia, and obesity [61–63]. Lifestyle modification and minimization of immune suppressants can be effective in reducing these risks. In summary, liver transplantation gives children with a potentially lethal disease an excellent long-term prognosis and quality of life.

Conclusions and Future Directions

Long-term outcomes for infants and children undergoing LT are excellent and have improved over time. The history of pediatric LT has clearly shown that success is dependant on constant collaboration between pediatricians, hepatologists, surgeons, nurses, transplant coordinators, dieticians, psychologists and social workers. The incidence of acute and chronic rejection has fallen following the development of newer immunosuppressive drugs and protocols. One major problem remains the lack of donors. In the U.S. the total number of pediatric liver donor has decreased in 10 years from 20 to 12 % [64]. Donation after cardiac death offers a new possibility to increase the pool of potential donors [40, 65]. In children with acute liver failure, increasing interest has centred on the possibility of providing temporary liver support based on extracorporeal devices (artificial and bioartificial) or on hepatocyte transplantation, either as a bridge to liver transplantation or ideally to obviate the need for it. Similarly, hepatocyte transplantation offers new perspective in infants and children with metabolic failure. As long-term survival increases, attention has now focused on the quality of life achieved by children undergoing transplantation [5, 13, 57, 66].

References

1. Kamath BM, Olthoff KM. Liver transplantation in children: update 2010. Pediatr Clin North Am. 2010;57:401–14.
2. Kelly DA. Current issues in pediatric transplantation. Pediatr Transplant. 2006;10(6):712–20.
3. Martin SR, Atkison P, Anand R, et al. Studies of pediatric liver transplantation 2002: patient and graft survival and rejection in pediatric recipients of a first liver transplant in the United States and Canada. Pediatr Transplant. 2004;8(3):273–83.
4. Berg CL, Steffick DE, Edwards EB, et al. Liver and intestine transplantation in the United States 1998–2007. Am J Transplant. 2009; 9(4 Pt 2):907–31.
5. Dommergues JP, Letierce A, Gravereau L, et al. Current lifestyle of young adults after liver transplantation during childhood. Am J Transplant. 2010;10:1643–51.
6. Fouquet V, Alves A, Branchereau S, et al. Long-term outcome of pediatric liver transplantation for biliary atresia: a 10-Year follow-up in a single center. Liver Transpl. 2005;11:152–60.
7. Ng VL, Fecteau A, Shepherd R, et al. Outcomes of 5 year survivors of pediatric liver transplantation: report on 461 children from a North American multicenter registry. Pediatrics. 2008;122(6):e 1128–35.
8. Otte JB. History of pediatric liver transplantation. Where are we coming from? Where do we stand ? Pediatr Transplant. 2002; 6(5):378–87.
9. McDiarmid SV, Anand R, Martz BS, Millis MJ, Mazariegos G. A multivariate analysis of pre-, peri-, and post-transplant factors affecting outcome after pediatric liver transplantation. Ann Surg. 2011;254:145–54.
10. Narkewicz MR, Dell Olio D, Karpen SJ, et al. Pattern of diagnostic evaluation for the causes of pediatric acute liver failure: an opportunity for quality improvement. J Pediatr. 2009;155(6):801–6. e801.

11. Ng V, Anand R, Martz K, et al. Liver retransplantation in children: a SPLIT database analysis of outcome and predictive factors for survival. Am J Transplant. 2008;8(2):386–95.
12. Diamond IR, Fecteau A, Millis JM, et al. Impact of graft type on outcome in pediatric liver transplantation: a report from Studies of Pediatric Liver transplantation (SPLIT). Ann Surg. 2007;246(2):301–10.
13. Duffy JP, Kao K, Co CY, et al. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. Ann Surg. 2010;252:652–61.
14. Duffy JP, Hong JC, Farmer DG, et al. Vascular complications of orthotopic liver transplantation: experience in more than 4,200 patients. J Am Coll Surg. 2009;208:896–905.
15. Hong JC, Yersiz H, Farmer DG, et al. Longterm outcomes for whole and segmental liver grafts in adult and pediatric liver transplant recipients: a 10-year comparative analysis of 2,988 cases. J Am Coll Surg. 2009;208:682–91.
16. Spada M, Maggiore G, Cintorino D, Gridelli B. Pediatric liver transplantation. World J Gastroenterol. 2009;15:648–74.
17. McDiarmid SV, Anan R, Lindblad AS, SPLIT Research Group. Studies of pediatric liver transplantation: 2002 update. An overview of demographics, indications, timing, and immunosuppressive practices in pediatrics transplantation in the United States and Canada. Pediatr Transplant. 2004;8:284–94.
18. Durand P, Debray D, Mandel R, et al. Acute liver failure in infancy: a 14-year experience of a pediatric liver transplantation center. J Pediatr. 2001;139:871–6.
19. Florman S, Shneider B. Living-related liver transplantation in inherited metabolic liver disease: feasibility and cautions. J Pediatr Gastroenterol Nutr. 2001;33(4):520–1.
20. Kayler LK, Rasmussen CS, Dykstra DM, et al. Liver transplantation in children with metabolic disorders in the United States. Am J Transplant. 2003;3(3):334–9.
21. Sze YK, Dhawan A, Taylor RM, et al. Pediatric liver transplantation for metabolic liver disease: experience at King's College Hospital. Transplantation. 2009;87(1):87–93.
22. Treem WR. Liver transplantation for non-hepatotoxic inborn errors of metabolism. Curr Gastroenterol Rep. 2006;8(3):215–23.
23. Squires Jr RH, 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(5):652–8.
24. Devictor D, Tissieres P, Afanetti M, Debray D. Acute liver failure in children. Clin Res Hepatol Gastroenterol. 2011;35:430–7.
25. Devictor D, Desplanques L, Debray D, et al. Emergency liver transplantation for fulminant liver failure in infants and children. Hepatology. 1992;16:1156–62.
26. Farmer DG, Venick RS, McDiarmid SV, et al. Fulminant hepatic failure: superior and durable outcomes with liver transplantation over 25 years at a single center. Ann Surg. 2009;250:484–93.
27. Shanmugam NP, Bansal S, Greenough A, Verma A, Dhawan A. Neonatal liver failure: aetiologies and management-state of the art. Eur J Pediatr. 2011;170:573–81.
28. Futagawa Y, Terasaki P. An analysis of the OPTN/UNOS liver transplant registry. Clin Transplant. 2004;18:315–29.
29. Baliga P, Alvarez S, Lindblad A, et al. Postransplant survival in pediatric fulminant hepatic failure: the SPLIT experience. Liver Transpl. 2004;10(11):1364–71.
30. 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;6:585–91.
31. Austin MT, Leys CM, Feurer ID, et al. Liver transplantation for childhood hepatic malignancy: a review of the United Network for Organ Sharing (UNOS) database. J Pediatr Surg. 2006;41(1):182–6.
32. Avila LF, Luis AL, Hernandez F, et al. Liver transplantation for malignant tumours in children. Eur J Pediatr Surg. 2006;16(6):411–4.
33. Barshes NR, Chang IF, Karpen SJ, et al. Impact of pretransplant growth retardation in pediatric liver transplantation. J Pediatr Gastroenterol Nutr. 2006;43(1):89–94.
34. Freeman Jr RB, Wiesner RH, Harper A, et al. The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl. 2002;8(9):851–8.
35. McDiarmid SV, Merion RM, Dykstra DM, et al. Selection of pediatric candidates under the PELD system. Liver Transpl. 2004;10(10 Suppl 2):S23–30.
36. Wiesner RH, Mc Diarmid SV, Kamath PS, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl. 2001;7(7):567–80.
37. Becker NS, Barshes NR, Aloia TA, et al. Analysis of recent pediatric orthotopic liver transplantation outcomes indicates that allograft type is no longer a predictor of survivals. Liver Transpl. 2008;14(8):1125–32.
38. Roberts JP, Hulbert-Shearon TE, Merion RM, et al. Influence of graft type on outcomes after pediatric liver transplantation. Am J Transplant. 2004;4(3):373–7.
39. Strong RW, Lynch SV, Ong TH, et al. Successful liver transplantation from a living donor to her son. N Engl J Med. 1990;322(21):1505–7.
40. Abt PL, Fisher CA, Singhal AK. Donation after cardiac death in the US: history and use. J Am Coll Surg. 2006;203(2):208–25.
41. Farmer DG, Venick RS, McDiarmid SV, et al. Predictors of outcomes after pediatric liver transplantation: an analysis of more than 800 cases performed at a single institution. J Am Coll Surg. 2007;204:914–6.
42. Bourdeaux C, Darwish A, Jamart J, et al. Living related versus deceased donor pediatric liver transplantation: a multivariate analysis of technical and immunological complications in 235 recipients. Am J Transplant. 2007;7:400–7.
43. Kim JS, Grotelüschen R, Mueller T, et al. Pediatric transplantation: the Hamburg experience. Transplantation. 2005;79:1206–9.
44. Ueda M, Oike F, Ogura Y, et al. Long-term outcomes of 600 living donor liver transplantations for pediatric patients at a single center. Liver Transpl. 2006;12:1326–36.
45. Heaton N, Faraj W, Melendez HV, et al. Living related liver transplantation in children. Br J Surg. 2008;95:919–24.
46. Tiao GM, Alonso M, Bezerra J, et al. Liver transplantation in children younger than 1 year-the Cincinnati experience. J Pediatr Urg. 2005;40(1):268–73.
47. Peclet MH, Ryckman FC, Pedersen SH, et al. The spectrum of bile duct complications in pediatric liver transplantation. J Pediatr Surg. 1994;29(2):214–9; discussion; 219–20.
48. Sunku B, Salvalaggio PR, Donaldson JS, et al. Outcomes and risk factors for failure of radiologic treatment of biliary strictures in pediatric liver transplantation recipients. Liver Transpl. 2006;12(5):821–6.
49. Tiao GM, Alonso MH, Ryckman FC. Pediatric liver transplantation. Semin Pediatr Surg. 2006;15(3):218–27.
50. Bourdeaux C, Brunati A, Janssen M, et al. Liver retransplantation in children. A 21-year single-center experience. Transpl Int. 2009;22(4):416–22.
51. Hubscher S. What does the long-term liver allograft look like for the pediatric recipient? Liver Transpl. 2009;15 Suppl 2:S19–24.
52. Venick RS, Mc Diarmid SV, Farmer DG, et al. Rejection and steroid dependence: unique risk factors in the development of pediatric post-transplant de novo auto-immune hepatitis. Am J Transplant. 2007;7(4):955–63.
53. Evans HM, Kelly DA, Mc Kiernan PJ, et al. Progressive histological damage in liver allografts following pediatric liver transplantation. Hepatology. 2006;43(5):1109–17.
54. Venick RS, Farmer DG, McDiarmid SV, et al. Predictors of survival following liver transplantation in infants: a single-center analysis of more than 200 cases. Transplantation. 2010;89:600–5.

55. Grabhorn E, Richter A, Fischer, et al. Emergency liver transplantation in neonates with acute liver failure: long-term follow-up. Transplantation. 2008;86(7):932–6.
56. Sundaram SS, Alonso EM, Anand R. Outcomes after liver transplantation in young infants. J Pediatr Gastroenterol Nutr. 2008; 47(4):486–92.
57. Bell LE, Bartosh SM, Davis CL, et al. Adolescent transition to adult care in solid organ transplantation: a consensus conference report. Am J Transplant. 2008;8(11):2230–42.
58. Shemesh E. Non-adherence to medications following pediatric liver transplantation. Pediatr Transplant. 2004;8(6):600–5.
59. Alonso EM, Shepherd R, Martz KL, et al. Linear growth patterns in prepubertal children following liver transplantation. Am J Transplant. 2009;9(6):1389–97.
60. Campbell KM, Yazigi N, Rychman FC, et al. High prevalence of renal dysfunction in long-term survivors after pediatric liver transplantation. J Pediatr. 2006;148(4):475–80.
61. Everhart JE, Lombardero M, Lake JR, et al. Weight change and obesity after liver transplantation: incidence and risk factors. Liver Transpl Surg. 1998;4(4):285–96.
62. Hathout E, Alonso E, Anand R, et al. Post-transplant diabetes mellitus in pediatric liver transplantation. Pediatr Transplant. 2009;13(5):599–605.
63. Varo E, Padin E, Otero E, et al. Cardiovascular risk factors in liver allograft recipients: relationship with immunosuppressive therapy. Transplant Proc. 2002;34(5):1553–4.
64. Magee JC, Krishnan SM, Benfield MR, et al. Pediatric transplantation in the United States, 1997–2006. Am J Transplant. 2008;8:935–45.
65. Naim MY, Hoehn KS, Hasz RD, et al. The Children's Hospital of Philadelphia's experience with donation after cardiac death. Crit Care Med. 2008;36(6):1729–33.
66. Soltys KA, Mazariegos GV, Squires RH, et al. Late graft loss or death in pediatric liver transplantation: an analysis of the SPLIT database. Am J Transplant. 2007;7(9):2165–71.