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doi:10.3748/wjg.15.648

World J Gastroenterol 2009 February 14; 15(6): 648-674
World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

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Pediatric liver transplantation

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Received: July 4, 2008 Revised: December 3, 2008
Accepted: December 10, 2008
Published online: February 14, 2009

Abstract

In previous decades, pediatric liver transplantation has become a state-of-the-art operation with excellent success and limited mortality. Graft and patient survival have continued to improve as a result of improvements in medical, surgical and anesthetic management, organ availability, immunosuppression, and identification and treatment of postoperative complications. The utilization of split-liver grafts and living-related donors has provided more organs for pediatric patients. Newer immunosuppression regimens, including induction therapy, have had a significant impact on graft and patient survival. Future developments of pediatric liver transplantation will deal with long-term follow-up, with prevention of immunosuppression-related complications and promotion of as normal growth as possible. This review describes the state-of-the-art in pediatric liver transplantation.

Key words: Pediatric liver transplantation; Indications; Surgical techniques; Complications

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Spada M, Riva S, Maggiore G, Cintorino D, Gridelli B. Pediatric liver transplantation. *World J Gastroenterol* 2009; 15(6): 648-674 Available from: URL: http://www.wjgnet.com/1007-9327/15/648.asp DOI: http://dx.doi.org/10.3748/wjg.15.648

INTRODUCTION

Liver transplantation has been very successful in treating children with end-stage liver disease, and offers the opportunity for a long healthy life. Organ scarcity, which is the main limitation to the full exploitation of transplantation, is being overcome thanks to innovative surgical techniques, and all children in need, even the youngest, today have the chance of being transplanted, with almost no waiting list mortality. Split-liver and living-donor transplantation have contributed to reversing a situation in which, during the 1980s and 90s, children had greater waiting list mortality compared to that of adult patients.

Several years ago, the main focus of care of children with end-stage liver disease was to find a liver transplant, but today, the main interest is in long-term follow-up, with prevention of immunosuppression-related complications and promotion of as normal growth as possible. The history of pediatric liver transplantation has clearly shown that success is dependent on strict and integrated collaboration between referring pediatricians, pediatric transplant hepatologists, transplant surgeons, nurses, transplant coordinators, psychologists and social workers. Everybody involved has the task of bringing a cure to a population of pediatric patients who present some of the most challenging clinical problems in modern medicine.

INDICATIONS FOR LIVER TRANSPLANTATION

The main indications for liver transplantation in the pediatric population are as follows: (1) Extra-hepatic cholestasis: biliary atresia. (2) Intra-hepatic

cholestasis: sclerosing cholangitis; Alagille's syndrome; non-syndromic paucity of intrahepatic bile ducts; and progressive familial intrahepatic cholestasis. (3) Metabolic diseases: Wilson's disease; α_1-antitrypsin deficiency; Crigler-Najjar syndrome; inborn error of bile acid metabolism; tyrosinemia; disorders of the urea cycle; organic acidemia; acid lipase defect; oxaluria type Ⅰ; and disorders of carbohydrate metabolism. (4) Acute liver failure. (5) Others: primary liver tumor and cystic fibrosis.

Cholestatic liver diseases

Typically, the child referred to a liver transplant center is a small baby with cholestatic liver disease. Out of 1187 children transplanted in North America between 1995 and May 2002, 33.5% were ⩽ 12 mo 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[1]. Most of these children have undergone a Kasai procedure that failed to re-establish effective biliary flow, which caused rapid evolution to secondary biliary cirrhosis. When intrahepatic cholestatic diseases (Alagille's syndrome, progressive familial intrahepatic cholestasis, and sclerosing cholangitis) or sclerosing cholangitis are diagnosed, liver transplantation is indicated to eliminate severely debilitating symptoms, such as pruritus. Children affected by these diseases are also at high risk for the development of liver cancer[2].

Metabolic diseases

Metabolic diseases are the second most common indication for liver transplantation[3]. Metabolic diseases can be divided in two groups on the basis of the presence or absence of structural damage of the liver. To the first group belong α_1-antitripsin deficiency, tyrosinemia and Wilson's disease, which have the potential to progress to end-stage liver failure, liver cancer (Figure 1) and acute liver failure, while diseases such as Crigler-Najjar syndrome type Ⅰ and ornithine transcarbamylase (OTC) deficiency belong to the second group. In primary hyperoxaluria type Ⅰ, liver and kidney transplantation is considered when irreversible kidney damage from oxalic acid accumulation has developed. Different transplantation timings have been tested, combined liver and kidney transplantation (simultaneous or sequential) and pre-emptive liver transplantation (before end-stage renal failure occurs)[4,5]. Liver transplantation has been suggested recently for the treatment of organic acidemia (propionic aciduria, methylmalonic aciduria). In patients affected by these diseases, liver transplantation does not correct the enzyme deficiency in other organs beside the liver. Although quality of life is generally improved, patients remain at risk of severe extrahepatic disease complications[6-8]. Liver cirrhosis with severe portal hypertension develops in an about 25% of the patients affected by cystic fibrosis. Liver transplantation should be considered before the development of end-stage liver failure and when pulmonary function is still preserved (FEV_1 > 50%).

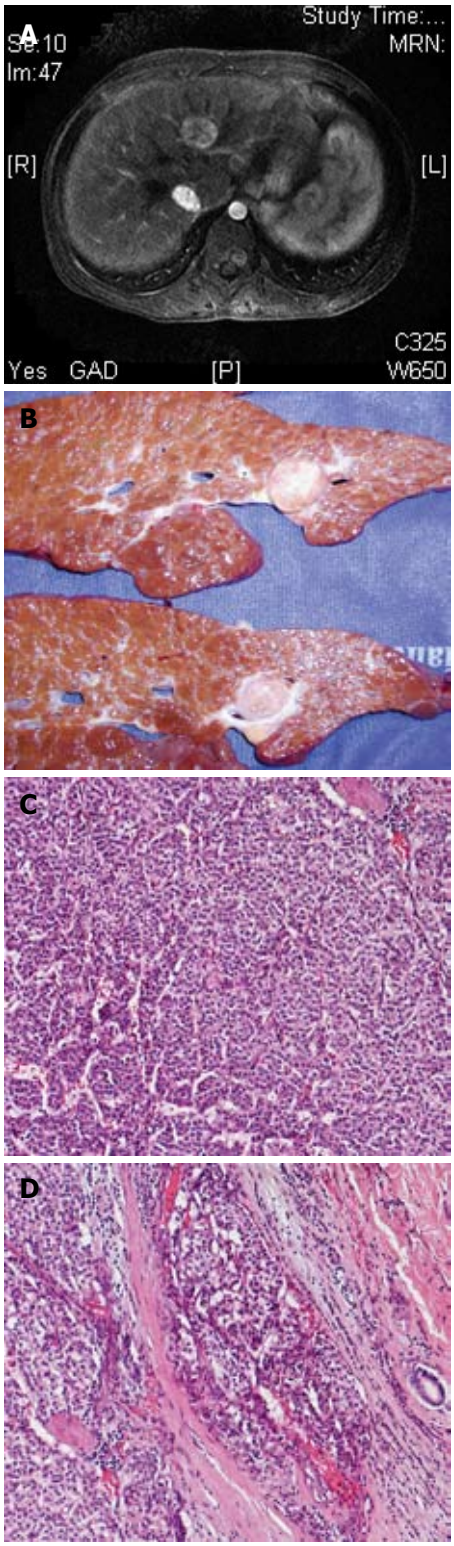

Figure 1 Adolescent affected by tyrosinemia who developed hepatocellular carcinoma, despite 2-(2-nitro-4-fluoromethylbenzoyl)-1,3-cyclohexanedione therapy. A: Magnetic resonance imaging displays a 26-mm lesion. B: After liver transplantation, the resected liver showed multiple nodules in the left lobe. C: Histological sections from the nodule revealed hepatocellular carcinoma. D: Microvascular invasion.

Acute liver failure

Acute liver failure is a rare event in children; recovery without transplantation occurs in 15%-20% of patients with severe hepatic encephalopathy. A prospective study from the Pediatric Acute Liver Failure Study Group

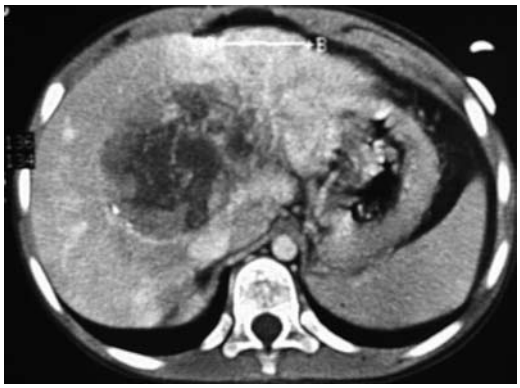

Figure 2 Non-resectable hepatoblastoma.

has indicated that in 49% of patients (54% of children aged 1 year), the cause of acute liver failure cannot be determined and that total bilirubin ⩾ 5 mg/dL, international normalized ratio (INR) ⩾ 2.55 and hepatic encephalopathy are risk factors predictive of death or liver transplantation[9]. In a large retrospective United Network for Organ Sharing (UNOS) data analysis, it has been shown that 5-year patient and graft survivals of children with acute liver failure are significantly lower than the survival of children transplanted for biliary atresia (73% and 59% *vs* 89% and 78%, respectively)[10].

Liver tumors

Hepatoblastoma is the most common liver tumor in children and, when non-resectable, should be treated with total hepatectomy and liver transplantation (Figure 2). Children with hepatoblastoma should first be treated with chemotherapy and then be evaluated for resection or transplantation[11]. Hepatocellular carcinoma in children is rare and is often secondary to congenital liver disease. The development of hepatocellular carcinoma has been reported in biliary atresia, Alagille's syndrome, progressive intrahepatic cholestasis (recently also hepatoblastoma has been reported in a child with this condition). In children with tyrosinemia, there is 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 (NBTC) therapy.

CONTRAINDICATIONS TO LIVER TRANSPLANTATION

Current contraindications to liver transplantation in children are: (1) non-resectable extrahepatic malignant tumor; (2) concomitant end-stage organ failure that cannot be corrected by a combined transplant; (3) uncontrolled sepsis; and (4) irreversible serious neurological damage. Whereas in adults there are limitations to access to liver transplantation waiting lists for patients with primary liver tumors, in children, the approach is much more liberal and the indication should be discussed on a case by case analysis with pediatric oncologists.

EVALUATION OF THE TRANSPLANT CANDIDATE

The primary goal of the evaluation process is to identify appropriate candidates for liver transplantation and to establish a pre-transplantation plan. The following steps are usually considered: (1) confirm the indication for transplantation; (2) determine the severity of the disease; (3) consider alternative treatments to transplantation; (4) exclude contraindications to transplantation; (5) identify active infections and assess the immunological status of the child; (6) rule out cardiac malformations that might need to be corrected before transplantation; (7) establish a pre-transplant therapeutic plan: immunizations, when possible, nutritional support to optimize growth, dental care, prevention or treatment of drug-induced side effects (e.g. osteopenia secondary to prolonged steroid intake); (8) inform parents, and the patient if possible, on the transplantation procedure and on the post-transplantation period in order to motivate and prepare them to accept and deal with all issues and possible complications of the procedure; and (9) evaluate social status and logistic issues.

PRIORITIZATION

In the early 1980s, waiting time and severity of illness expressed by patient location (home, hospital, ICU) were the primary factors used to stratify patients. Later on, it was shown that waiting time had no relationship to mortality, except for urgent acute liver failure patients, and therefore, that an allocation policy based on objective medical criteria was needed. Based on data derived from the Studies of Pediatric Liver Transplantation research group, a pediatric end-stage liver disease score (PELD) was created, using bilirubin, INR, serum albumin, age > 1 year, and growth failure to predict waiting list mortality[12]. Additional PELD points are awarded for specific risk factors not taken into account in the PELD equation, 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. However, the PELD score has not proven to be a successful predictor of outcome following transplantation[13,14].

THE TRANSPLANT OPERATION

The first liver transplant was performed by Thomas Starzl, in 1963, on a 2-year-old child affected by biliary atresia[15]. The patient died in the operating room of uncontrolled hemorrhage. After this first case, and up to the early 1980s, the only technical option for pediatric liver transplantation was to transplant the whole liver of a donor with a weight as close as possible to that of the recipient. Given the low number of pediatric donors, up to 50% of the children on the waiting list would die before they could receive a transplant[16]. The development of techniques that allow surgeons to transplant portions of livers from adult donors has

completely changed the fate of liver transplantation in pediatric patients.

Whole-liver transplantation

The procedure of whole-liver procurement in pediatric donors can be performed exactly as in adults, applying a technique that is a combination of the initial procurement technique described by Starzl *et al*[17], and the most recently described rapid flush technique[18,19]. Whole-liver pediatric transplantation can be performed with two different techniques: the classic technique with inferior vena cava replacement, and the piggyback technique[20] with preservation of the native inferior vena cava. The present authors routinely use the classic technique in the vast majority of whole liver transplants. Veno-venous bypass is generally not used in pediatric liver transplantation, given that patients generally tolerate explantation well, provided that volume replacement has been adequate. Adopted techniques are almost identical to the ones used in adults recipients. In cases in which the liver is encased in adhesions, as it is in biliary atresia, we recommend that surgeons first approach the hepatic hilum from the right posterolateral aspect, identifying the Roux-en-Y jejunal limb, which is transected with a linear stapler or between ligatures. This allows better exposure and dissection of the hilum. If the portal vein is small and sclerotic, it has to be dissected proximally to the confluence of the splenic and superior mesenteric vein, dividing the coronary vein of the stomach. The portal vein anastomosis will then be performed by means of a donor interposition vein graft. In difficult dissections, the vena cava can be clamped above and below the liver before completing the mobilization of the liver itself.

Several methods of arterial reconstruction have been proposed. It is our preference to anastomose the small arterial vessels encountered in pediatric whole liver transplantation in an end-to-end manner by using the magnification loops (3.5 ×) and interrupted or running 8-0 polypropylene sutures. We generally do not use the branch patch technique, and in the case of aberrant arterial anatomy, the supraceliac aorta is the inflow vessel of choice. The use of arterial conduits anastomosed to the infrarenal aorta is avoided if possible.

In theory, biliary tract continuity can be restored through direct anastomosis between the new liver's hepatic duct and the recipient's common bile duct. However, the most common type of biliary reconstruction adopted in pediatric patients is hepaticojejunostomy. In biliary atresia patients, the reconstruction uses the previous Roux-en-Y limb of the hepatic portoenterostomy, if suitable; otherwise a 40-cm Roux-en-Y jejunal limb is created. The authors' attitude is not to use a T tube, because no randomized trial so far has demonstrated any advantages in using it, and there are often biliary leaks when the T tube is pulled.

Occasionally in children, abdominal-wall closure may be impossible because of the large size of the transplanted liver. This may be remedied by creating a silo on the abdominal wall such that a temporary closure can be made[21].

Reduced-size liver transplantation

This procedure was first described by Bismuth *et al*[22] and consists in the procurement of the whole liver from an adult cadaver donor, which is reduced in its size on the back-table. In the original description, a right hepatectomy was performed on the back-table: the right lobe of the liver was discharged, while the left lobe (Couinaud liver segments 1 to 4), including the vena cava, was transplanted in a child. This technique of parenchymal reduction, very seldom used today, allows surgeons to overcome differences in size between the donor and the recipient of up to four or five times[23,24].

Following these first experiences, a more aggressive reduction that allows transplanting the liver from donors with a body weight up to 12 times the recipient's was introduced. On the back-table, the graft undergoes an extended right hepatectomy, including segment 4 and the caudate lobe. The resulting left lateral segment graft comprises segments 2 and 3, without the vena cava. The graft is transplanted retaining the recipient's vena cava, anastomosing the graft left hepatic vein to the recipient's vena cava.

Reduced-size liver transplantation shows outcomes in line, if not superior, to whole-liver transplantation, and has become an essential part of the technical expertise of pediatric transplant centers[25-30] (Table 1). The development of this technique has led to almost total elimination of child mortality on the waiting list, through the utilization of an adult liver cadaver donor. Its main limitation is that it withdraws organs from the larger adult recipient pool. For this reason, after the development of living-related and split-liver transplantation, reduced-size live transplantation is used increasingly less, and should not be considered an option anymore for pediatric liver transplantation.

Living-related liver transplantation

The first description of the procedure in which segments 2 and 3 were procured from a living donor (the mother), and transplanted in a child affected by biliary duct atresia, dates back to 1988[31,32]. Living-related liver transplants soon came to account for a substantial number of pediatric cases performed in many centers throughout the world, and the only possibility for liver transplants in countries where cadaveric organ procurement was not allowed until just a few years ago[33].

Living-donor procurement involves performing a left lobectomy during which segments 2 and 3 are separated from the remaining liver, and dissecting the parenchyma along a section running to the right of the round ligament. After the parenchyma dissection, the left branch of the portal vein, the hepatic artery, and the left suprahepatic vein are quickly clamped and dissected, and the left lobe perfused on the back-table. The recipient's procedure is similar to the one described for the transplant of segments 2 and 3 from a cadaver donor, except for the fact that the arterial anastomosis can be performed only in the left branch of the hepatic artery. The branch is small and usually anastomosed directly to the recipient's hepatic artery using the operative

Table 1 Series of pediatric reduced-size liver transplantation

Series	Period	*n*	Survival (%)		ReTX (%)	Complications (%)			
			Patient	Organ		HAT	PVT	BC	PNF
Broelsch *et al*[25]	1984-1987	9	44	33	11	0	0	11	11
Otte *et al*[26]	1984-1988	42	68	54	28	7	0	NA	5
Bismuth *et al*[22]	1984-1988	14	50	44	14	7	7	14	7
Houssin *et al*[27]	1986-1989	40	75	73	-	5	5	5	5
Kalayoglu *et al*[28]	1988-1989	12	83	67	25	16	8	0	0
Esquivel *et al*[29]	1988-1990	20	81	75	12	0	3	5	0
Langnas *et al*[30]	1988-1991	29	68	65	3	7	0	20	10

ReTX: Retransplantation; HAT: Hepatic artery thrombosis; PVT: Portal vein thrombosis; BC: Biliary complication; PNF: Primary non-function; NA: Not available.

Table 2 Series of pediatric living-related liver transplantation

Series	Period	*n*	Survival (%)		ReTX (%)	Complications (%)			
			Patient	Organ		HAT	PVT	BC	PNF
Tanaka *et al*[33]	1990-1992	37	E 90 U 57	E 90 U 57	0	U 14	E 3	E 10	0
Emond *et al*[34]	1991-1992	18	94	84	16	11	6	16	0
Broelsch *et al*[35]	1991	20	85	75	20	25	20	35	0
Malagò *et al*[36]	1991-1994	36	72	72	8	2.8	3	25	-
Otte *et al*[37]	1993-1995	30	97	93	-			20	
Haberal *et al*[38]	1990-1997	19	58	58	0	5	0	0	0
Darwish *et al*[39]	1993-2002	100	94	92	3	1	14	27	0

E: Elective cases; U: Urgent cases; ReTX: Retransplantation; HAT: Hepatic artery thrombosis; PVT: Portal vein thrombosis; BC: Biliary complication; PNF: Primary non-function.

microscope.

Living-related liver transplantation has been widely debated with regard to the ethics of performing major surgery on a healthy person. The validity of this procedure is broadly recognized, and over 1200 cases have been performed worldwide, with a donor mortality and morbidity of approximately 0.2% and 10%, respectively. Morbidity relates mainly to biliary fistulas, incisional hernias, and bleeding. In the majority of cases, living-related transplants register an excellent outcome for pediatric recipients, thanks to the possibility of performing the transplant before the child's clinical condition deteriorates. Centers with most experience in this area report survival rates between 80 and 90% after 1 year[34-39] (Table 2).

Split-liver transplantation

Split-liver transplantation, as described originally by Pichlmayr, involves procuring a whole liver from a cadaver donor and dividing it into two sections along the round ligament, leaving the vascular structures for the two portions of hepatic parenchyma intact[40]. In this way, two partial organs are obtained from a single liver: the left lateral segment (segments 2 and 3), which can be transplanted in a child, and the extended right liver (segments 1 and 4-8), which can be transplanted into an adult. This procedure involves a much longer ischemia time, which, at the beginning of its adoption, led to unsatisfactory results, with a high incidence of primary dysfunction and technical complications[41-55] (Table 3). In 1994, Rogiers described a technical variation in the split-liver technique, derived from the living-related transplant experience that consisted in dividing the liver *in situ* during the procurement procedure[56]. The technique has shown outcomes comparable to those obtained with conventional techniques[57-62] (Table 4).

The donor operation

A section of the liver is made along the falciform ligament to obtain a left graft, composed of segments 2 and 3, including the left hepatic vein, the left branch of the portal vein, and the left branch of the hepatic artery, along with the common hepatic artery and the celiac tripod, and a right graft, composed of segments 1 and 4 to 8, including the vena cava, the right branch of the hepatic artery, and the portal vein along with the origin of the mesenteric and splenic veins (Figure 3).

At the beginning of the split procedure, the hepatogastric ligament is inspected to detect an accessory left hepatic artery originating from the left gastric artery, which must be preserved. When this vessel is not detected, the ligament is sectioned. The common hepatic artery is then identified and dissected from the gastroduodenal artery up to its division into the right and left hepatic arteries. The left hepatic artery is then encircled (Figure 4A). If present, branches for the fourth segment originating from the left hepatic artery should be identified and divided. The base of the round ligament is exposed by dividing the small bridge of parenchyma that connects the lower portion of segment 4 to the left lateral section of the liver. The round ligament is dissected and completely mobilized with isolation and division of its venous connections to the fourth segment. Once the round ligament is dissected, the extrahepatic portion of the left branch of the portal vein can be identified just below the left hepatic artery.

Table 3 Series of *ex situ* split-liver transplantation

Series	Year	ADU (*n*)	PED (*n*)	Urgent (%)	Patient survival (%)		Graft survival (%)		Complications (%)			
					ADU	PED	ADU	PED	HAT	PVT	BC	PNF
Pichlmayr *et al*[40]	1989	2	0	0	50	-	50	-	0	0	0	0
Bismuth *et al*[41]	1989	2	0	100	0	-	0	-	0	0	0	0
Otte *et al*[42]	1990	1	3	75	0	66	0	66	0	0	0	0
Emond *et al*[16]	1990	5	13	38	40	63	40	53	6	6	27	24
Broelsch *et al*[24]	1990	4	21	40	25	66	20	48	NA	NA	27	NA
Langnas *et al*[30]	1992	1	9	73	NA	NA	NA	NA	7	0	20	17
Houssin *et al*[43]	1993	6	10	50	83	70	83	60	13	25	25	0
Otte *et al*[44]	1994	11	18	27	NA	NA	NA	NA	10	0	17	10
Kalayoglu *et al*[45]	1996	5	7	8	100	85	80	71	8	0	17	0
Rogiers *et al*[46]	1996	5	7	44	57	100	42	100	15	0	15	0
Azoulay *et al*[47]	1996	26	1	14	80	100	76	100	15	0	22	4
Dunn *et al*[48]	1997	0	12	50		75		66	0	0	0	0
Rela *et al*[49]	1998	15	26	12	93	89	93	84	3	0	15	0
Mirza *et al*[50]	1998	10	14	58	80	78	NA	NA	8	0	8	16
Chardot *et al*[51]	1999	0	15	31	-	66	-	62	12	19	25	0
Reyes *et al*[52]	2000	13	12	66	69	66	61	50	12	0	8	NA
Deshpande *et al*[53]	2002	0	80	20	-	89	-	86	5	1	9	0
Noujaim *et al*[54]	2003	24	36	25	NA	NA	NA	NA	3	0	20	3
Oswari *et al*[55]	2005	0	30	13	-	70	-	67	2	5	7	NA

ADU: Adults; PED: Children.

Table 4 Series of *in situ* split-liver transplantation

Series	Year	ADU (*n*)	PED (*n*)	Urgent (%)	Patient survival (%)		Graft survival (%)		Complications (%)			
					ADU	PED	ADU	PED	HAT	PVT	BC	PNF
Rogiers *et al*[56]	1996	7	7	35	100	85	85	71	0	0	0	0
Goss *et al*[57]	1997	14	12	58	85	100	78	91	0	0	14	11
Busuttil *et al*[58]	1999	NA	NA	66	85	96	86	75	3	1	3	8
Ghobrial *et al*[59]	2000	51	51	49	83	78	NA	NA	2	2	NA	8
Reyes *et al*[52]	2000	NA	NA	NA	93	100	79	83	3	0	3	7
Spada *et al*[60]	2000	36	35	25	84	85	79	76	5	10	28	2
Gridelli *et al*[61]	2003	0	90	28	-	90	-	80	7	6	33	1
Yersiz *et al*[62]	2003	57	104	-	78	75	69	64	13	11	19	26

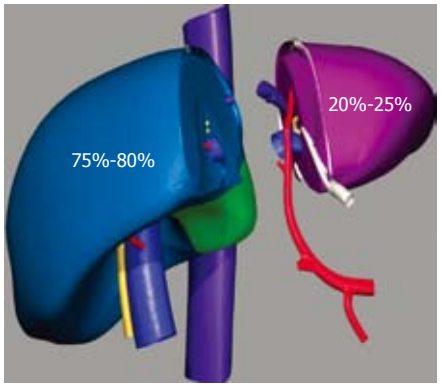

Figure 3 Spit liver allows for the procurement of two separate grafts of different size. A section of the liver is made along the falciform ligament and divides the left lateral segment from the extended right liver. The left graft, composed of segments 2 and 3, and representing 20%-25% of the total liver volume, includes the left hepatic vein, the left branch of the portal vein, and the left branch of the hepatic artery, along with the common hepatic artery and the celiac tripod. The right graft composed of segments 1 and 4-8, and representing 75%-80% of the total liver volume, includes the vena cava, the right branch of the hepatic artery, and the portal vein.

This vein must be carefully dissected and encircled (Figure 4B). The left lateral section is rotated laterally on the right side and the ligamentum venosum is dissected up to left lateral hepatic vein, which can be isolated and encircled (Figure 4C). The bile ducts of the left lateral segment are included in the porta hepatis and should not be dissected. On the contrary, the porta hepatis must be encircled and divided sharply (Figure 4D).

The section of the parenchyma can now be performed along the falciform ligament (Figure 4E). It is helpful when identifying the plane of the dissection to pass the cotton tape, which encircles the left hepatic vein on the posterior surface of the liver in the fossa of the ductus venosus, laterally to the left branch of the hepatic artery and of the portal vein (Figure 4F and G). Pulling up on this tape, the dissection of the parenchyma is usually easy. At this point, the procedure continues as a standard donor operation with heparinization, cannulation and cross-clamping of the aorta, perfusion, and cooling of the abdominal cavity. The left hepatic vein is then sectioned close to the vena cava. Care must be taken to identify a distal bifurcation of this vein. A double left hepatic vein significantly increases the technical difficulty of the implantation of the graft. In this case, the vessel should be removed with a cuff of vena cava to allow a single vascular anastomosis with

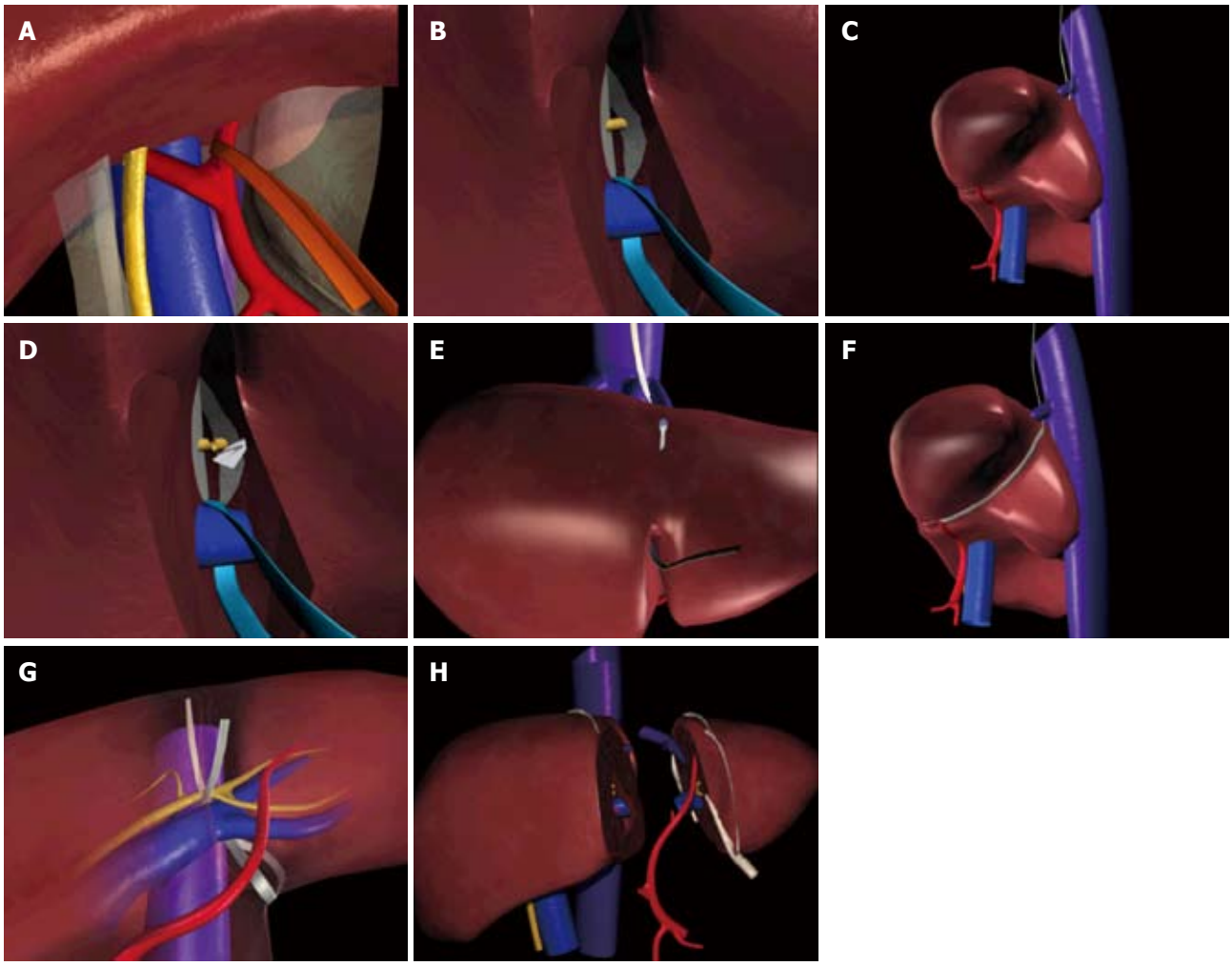

Figure 4 Main phases of split liver procurement. A: Dissection of the hepatogastric ligament and encircling of the left hepatic artery; B: Identification and encircling of the extrahepatic portion of the left branch of the portal vein; C: Isolation and encircling of the left hepatic vein; D: Division with a scalpel of the porta hepatis containing the bile duct(s) of the left lateral segment; E: Section of the parenchyma started along the falciform ligament; F: Identification of the plane of parenchymal dissection by passing the cotton tape, which encircled the left hepatic vein, on the posterior surface of the liver in the fossa of the ductus venosus; G: Laterally to the left branch of the hepatic artery and of the portal vein; H: The two partial grafts at the end of the procedure.

the recipient vena cava. The left branch of the portal vein is sectioned close to the parenchyma. The right hepatic artery is sectioned close to its origin, and the hepatic artery is dissected up to the celiac trunk, which is removed along with an aortic cuff.

The recipient operation

Recipient hepatectomy is performed, as previously described for whole-liver transplantation, with the piggy-back technique[63]. Implantation of the left lateral segment is substantially different from a whole-sized graft. Assuring an adequate venous outflow requires a careful technique of anastomosis between the left hepatic vein of the graft and the inferior vena cava of the recipient and a proper positioning of the graft itself, which is rotated clockwise 45° on a transversal plane and slightly on a frontal plane. The final position of the cut surface of the parenchyma, including the new hilum of the graft, is high and posterior, so that the portal vein and hepatic artery have a course that is curved and longer than usual.

The outflow anastomosis is end-to-side between the left hepatic vein of the graft and the inferior vena cava of the recipient, with the triangulation technique described by Emond *et al*[64]. The bridge between the ostia of the right and middle hepatic veins is cut to obtain a single opening. The ostium of the left hepatic vein may be treated in the same fashion, to obtain a further enlargement of the opening, or suture-closed. The opening is then enlarged by cutting the anterior face of the vena cava to obtain a wide reversed triangular orifice. The cuff of the left hepatic vein of the graft is trimmed as short as possible, to avoid kinking. Three 5/0 vascular monofilament sutures are placed, taking the three corners of the graft and recipient orifices (Figure 5). The graft is then placed in the hepatic fossa of the recipient and the triangular anastomosis performed with three running sutures.

The second anastomosis is the portal one, performed in an end-to-end fashion with running sutures of 6/0 or 7/0 vascular monofilament. Both the length and the section of the vessels are crucial. As already mentioned, the length should be sufficient for the vessel to make a gentle curve that reaches the hilum of the graft; as for

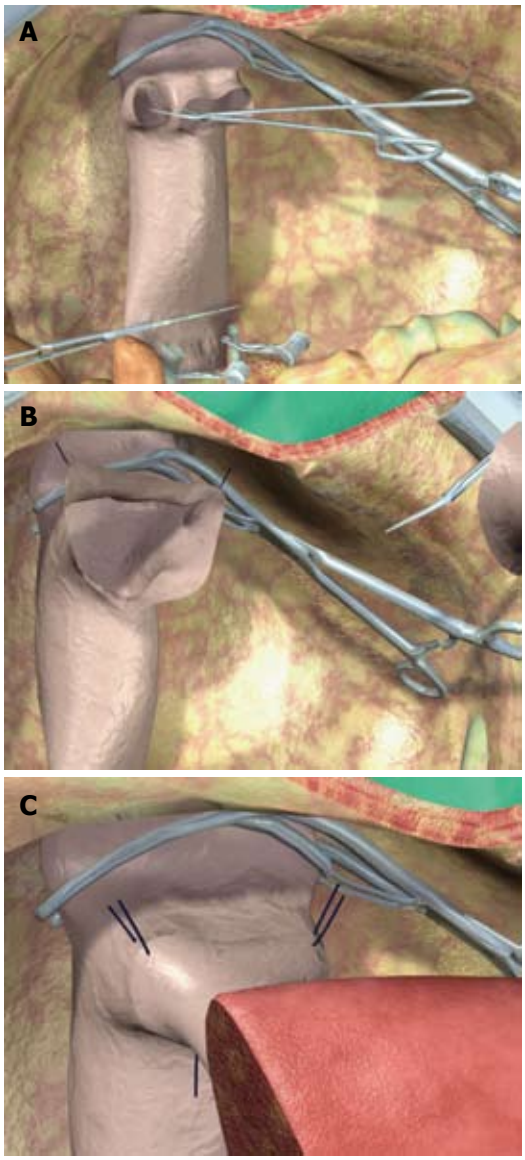

Figure 5 Anastomosis between the left hepatic vein of the graft and the inferior vena cava of the recipient, performed with the triangulation technique. A: The bridge between the ostia of the right, middle, and left hepatic veins is cut to obtain a single opening; B: The opening is further enlarged by cutting the anterior face of the vena cava to obtain a wide triangular orifice; C: Three 5/0 vascular monofilament sutures are placed, taking the three corners of the graft and recipient orifices.

the section, the limiting factor is the size of the graft cuff. In the majority of cases, the recipient's vessel matches this size rather well. If not, it can be cut at its bifurcation, to obtain a branch patch. In case of real hypoplasia of the recipient's portal vein, the confluence of the mesenteric and splenic vein can be clamped, the vessel sectioned at this level and a venous graft from the donor (usually the splenic or the external iliac vein) interposed between the confluence and the portal vein of the new liver. After completion of the anastomosis the graft is reperfused.

The arterial anastomosis comes next. The arterial axis of the graft usually includes the proper and common hepatic artery, in continuity with the celiac artery, and a patch of the aorta. The level of the anastomosis is chosen at any place along the recipient's arterial axis, and the two vessels are trimmed to obtain a similar section and an adequate length, according to what has already been stated concerning the portal vein. The anastomosis is performed end-to-end with a running suture of 7/0 or 8/0 vascular monofilament. If the recipient's arterial axis is deemed inadequate, the aorta can be clamped at the origin of the celiac artery or just below the renal arteries, and an end-to-side anastomosis can be performed at one of these sites. In the latter case, the interposition of an arterial graft from the donor, usually represented by an iliac artery, may be necessary.

The final stage is biliary reconstruction, which is always a hepaticojejunostomy with a Roux-en-Y loop. The bile duct of the graft may be single or double, although in the latter case two different anastomoses are performed (Figure 6).

Childhood hepatic malignancies have been considered a contraindication to the use of split-liver transplantation, since the need for the retention of the recipient's inferior vena cava potentially precludes obtaining a tumor-free margin[65]. A technical variation, which has allowed us and others to successfully use left lateral segment grafts to transplant children affected by hepatic malignancies, involves the replacement of the recipient's inferior vena cava using an iliac vein graft from the donor[66]. On the back-table, a wide V-shaped opening on the wall of the common iliac vein graft from the donor is made. The left hepatic vein of the left lateral segment graft is anastomosed end-to-side to the V-shaped opening on the common iliac vein with two 5/0 polypropylene running sutures (Figure 7). On the recipient, a total hepatectomy is usually performed using the standard technique of removing the liver together with the retrohepatic vena cava. At this point, the left lateral segment graft with the iliac vein graft is anastomosed to the suprahepatic vena cava in an end-to-end fashion with a 4/0 polypropylene running suture. The inferior edge of the iliac graft is then anastomosed to the infrahepatic vena cava with a 5/0 polypropylene running suture.

Donor selection

The following factors must be considered when a donor is evaluated for a specific patient.

Dimensional matching: The selection of a graft with an adequate parenchymal mass is critical to success. The minimal hepatic mass necessary for recovery is not clearly established, and its calculation must take into account the temporary loss of hepatocytes caused by the donor's injury or treatment, as well as preservation injury, acute rejection, or technical problems. Several formulas have been proposed to estimate adult and pediatric normal liver volume[67-72].

Considering that preservation injury is greater in organs from deceased donors, the hepatic mass of a graft procured from a cadaver donor should be greater than the calculated mass necessary using a living-donor liver segment. In the authors' experience, a donor weight range 20%-30% above or below that of the recipient is

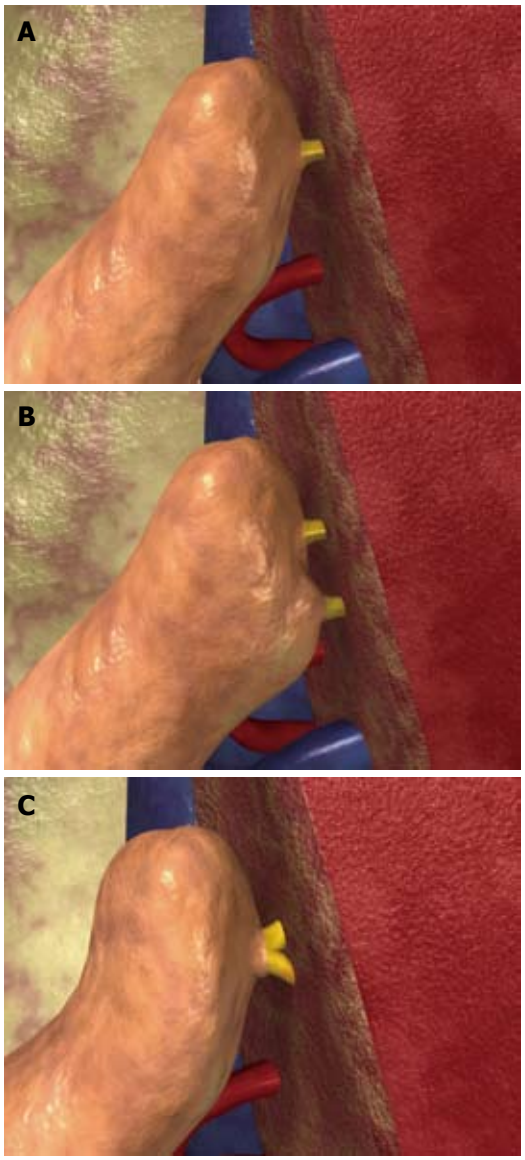

Figure 6 Biliary reconstruction performed by means of hepatico-jejunostomy. The bile duct of the graft can be single or double, although in the latter case, two different anastomoses are performed (B) or, if the two ducts are closed sufficiently, a common orifice can be created and anastomosed to the bowel loop (C).

ideal for whole-organ donors, however these values can be extended down to 50% below and 100% above, taking into consideration body habitus and factors that would increase recipient abdominal size, such as ascites and hepatosplenomegaly. When selecting donors of partial grafts, a graft fraction of 1%-3% of the recipient body mass is optimum, while a graft-to-recipient weight ratio < 0.7 is usually associated with inferior overall allograft and patient survival. In the authors' experience, a liver is procured and transplanted as a whole graft when the donor-to-recipient body weight ratio is ⩽ 2. When the donor-to-recipient body weight ratio is between 2 and 12, the graft is considered for split liver[60,61].

Donor characteristics: Donor-organ suitability is assessed by evaluating clinical information and by biochemical tests. Particular attention is paid to donor

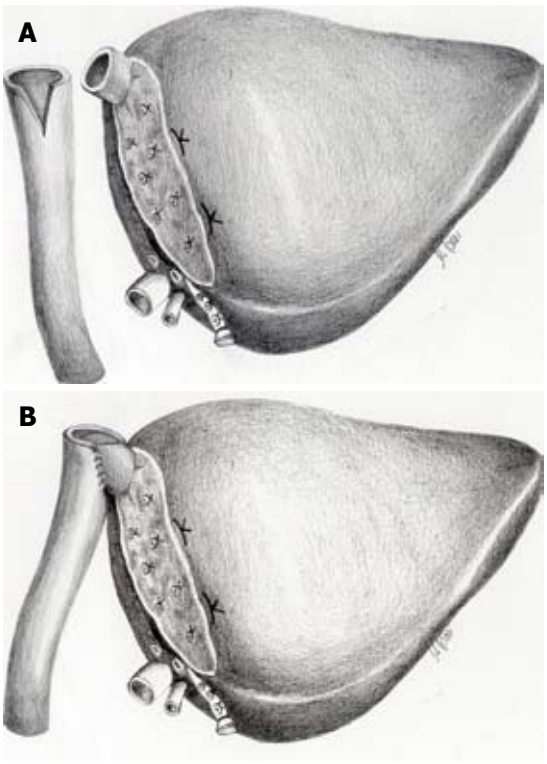

Figure 7 Use of left lateral segment grafts to transplant children affected by hepatic malignancies, with replacement of the recipient's inferior vena cava using an iliac vein graft from the donor. On the back table a wide V-shaped opening on the wall of the common iliac vein graft from the donor is made (A), and the left hepatic vein of the left lateral segment graft is anastomosed end-to-side to the V-shaped opening on the common iliac vein (B).

age, intensive care hospitalization time, infections, hemodynamic stability. Biochemical tests do not serve as good benchmarks of functional capability, even if severe electrolyte disturbances and deteriorating trends identify increased risk. In questionable cases, biopsy of the donor liver at the time of organ harvest or during evaluation of live donors is helpful to identify pre-existing liver disease or steatosis. Quite extended criteria can be used in donors of whole allografts, especially when ischemic time is limited, without compromising the outcome. On the contrary, restricted selection criteria have been proposed when split-liver transplantation is considered. Commonly accepted donor selection criteria for split-liver procurement are: (1) age 15-50 years; (2) weight > 40 kg; (3) no past history of liver dysfunction/damage; (4) liver function tests within 2-5-fold of normal values; (5) normal macroscopic appearance of the graft; and (6) hemodynamic stability[73]. Nevertheless, the authors have adopted a liberal policy of liver splitting. The decision of whether or not to split a graft is based mainly on recipient, rather than on donor, criteria. Children requiring re-transplantation or who have fulminant hepatic failure are not excluded. Donor evaluation does not require special or additional invasive or non-invasive tests. Using these extended criteria for donor selection, we have been able to transplant all the children in need with no mortality on the waiting list and good overall patient and graft survival rates[60,61].

No consistent data exist on the effect of donor age on the long-term results of pediatric liver transplantation. Data from multicenter registries have shown that pediatric patients receiving livers from pediatric-age donors have significantly better graft survival compared to those receiving livers from donors aged > 18 years[74,75]. These data strongly support the primary use of pediatric donors for pediatric recipients, but are not to be considered a contraindication to the use of adult donors in pediatric transplantation. The limited availability of pediatric donor organs does not allow us to satisfy the need of an increased waiting list population. Moreover, the results obtained using adult donors are biased by the policy to use older donors only in high-risk urgent cases. For split-liver transplantation, the authors used donors over the age of 50 years without affecting the 3-year patient and graft survival[76]. In addition, pediatric donors can be safely used for split-liver procurement and transplantation: left lateral segment is transplanted in a small child, while the extended right lobe can be used in larger children, adolescents or adults[77,78].

Living-donor selection: In living-donor transplantation, the evaluation and selection of a donor, usually a parent or first-degree relative is performed on the assumption that donor safety can be assured and that the donor's liver function is normal. Donors should be 18-55 years of age, and have an ABO-compatible blood type. Following a satisfactory medical and psychological examination by physicians who are not directly involved with the transplantation program, vascular imaging is performed to assess the hepatic arterial anatomy. Donor safety has been excellent in all living donor series.

EARLY POSTOPERATIVE PERIOD

The early postoperative period consists of managing problems related to technical complications and to the prevention, diagnosis, and treatment of acute rejection and infection episodes. Postoperative complications usually present with a combination of cholestasis, rising hepatocellular enzyme levels, and variable fever, lethargy and anorexia. This non-specific symptom complex requires specific diagnostic evaluation before establishing treatment, and empiric therapy may result in misdiagnosis, morbidity and mortality.

Primary non-function

The lack of graft functional recovery can be seen in the first hours following transplantation, with high lactate levels, increased prothrombin time and partial thromboplastin time, and failure of the patient to wake despite sedation suspension. This extremely serious complication must be treated aggressively and immediately by infusing prostaglandin E_1, adopting the necessary measures to prevent a brain edema (mannitol infusion, hyperventilation), and addressing the effects of the liver failure by infusing plasma and glucose. If the signs of lack of functional recovery persist for more than a few hours, the patient needs a new transplant as soon as possible. Lesser degrees of allograft dysfunction occur more frequently but are usually reversible. The status of the donor liver contributes significantly to the potential for primary non-function because of ischemic injury secondary to anemia, hypotension, hypoxia, or direct tissue injury. A possible cause of primary non-function is hyperacute rejection, a rare phenomenon characterized by rapid intraparenchymal vascular thrombosis, mediated by pre-formed antibodies that bind to the vascular endothelium and trigger the complement system. Antibodies are generally directed against protein alloantigens such as foreign MHC molecules or less differentiated alloantigens expressed on endothelial cells.

Vascular complications

The hepatic artery anastomosis carries the highest risk of thrombosis (5%-18%) and leads to massive graft necrosis in cases of early onset. Hepatic artery thrombosis occurs in children three to four times more frequently than in adult transplant patients, and occurs most often within the first 30 d after transplantation and in small babies transplanted with whole livers[62,79]. When hepatic artery thrombosis is identified early (Figure 8), reconstruction can be attempted to avoid allograft necrosis[80]. When allograft failure develops, urgent re-transplantation is the only option. Late thromboses (occurring some weeks after the transplant) can manifest with biliary complications (stenosis or dehiscence of the biliary anastomosis, intrahepatic bilomas) or sepsis. Rarely, allograft necrosis occurs. Stenosis of the hepatic artery usually occurs at the anastomosis and in many cases may progress to complete thrombosis. Clinical manifestations include cholestasis or graft failure caused by diminution in hepatic blood flow. Non-invasive diagnosis relies on Doppler ultrasound with calculation of resistive indices and systolic acceleration time. Treatment modalities include revision of the anastomosis or balloon angioplasty (Figure 9).

A typical complication of a left lateral segment graft is stenosis at the level of the anastomosis between the left hepatic vein of the graft and the native vena cava, which in the worst cases can lead to acute Budd-Chiari syndrome. However, since the introduction of the triangulation technique, this complication has become quite rare[68]. When present, outflow venous obstruction can be treated by cavography and balloon angioplasty (Figure 10).

Finally, portal vein thrombosis occurs in 5%-10% of recipients. It is more frequent in children transplanted for biliary atresia, because of pre-existing portal vein hypoplasia, which requires replacing the entire portal vein down to the confluence of the superior mesenteric vein with the splenic vein to avoid low-flow-related thrombosis. Early thrombosis following transplantation, detected by ultrasound screening, requires immediate anastomotic revision and thrombectomy[81]. Later thrombosis is usually detected by decreased platelet counts and increasing spleen size or gastrointestinal bleeding (Figure 11). Interventional radiographic stent

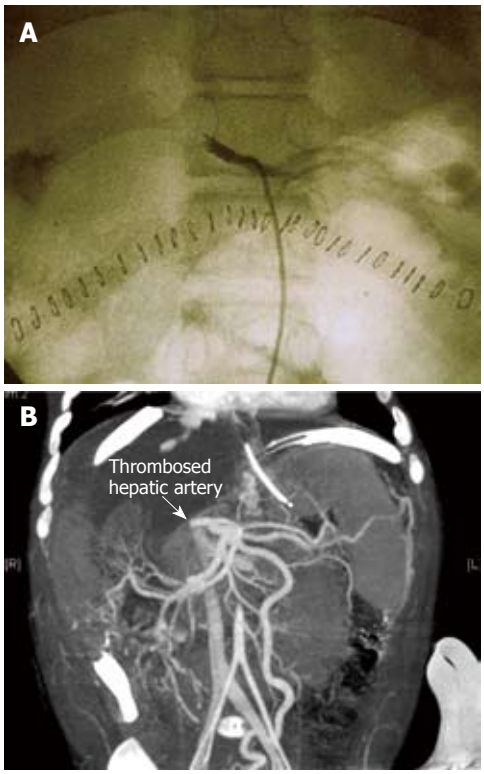

Figure 8 Selective celiac angiography showing early hepatic artery thrombosis after left lateral segment transplantation. A: Conventional angiography is the gold standard for radiographic diagnosis of hepatic artery thrombosis. B: Nowadays, the sensitivity of multiphase, multislice computed tomographic angiography with multidetector reconstruction approaches that of conventional angiography.

placement or balloon dilation has been successful in patients who have portal anastomotic stenosis but is less successful when complete thrombosis has occurred[82]. Portal venous shunting may be needed in patients who have progressive portal hypertensive complications.

Biliary complications

Biliary complications occur in approximately 10%-30% of pediatric liver transplant recipients, depending on the type of allograft used[62,83-85]. In the early postoperative period, the presence of bile-like fluid in the abdominal drainage is strongly suggestive of a bile leak. Ultrasound evidence of intrahepatic biliary ducts dilatation, elevated alkaline phosphatase and γ-glutamyl transferase (GT), and/or recurrent cholangitis suggest anastomotic or intrahepatic biliary stricture or small bowel obstruction at or distal to the Roux-en-Y anastomosis. Sometimes, non-specifically elevated liver function tests may be caused by a biliary stricture; in these cases a liver biopsy showing biliary duct proliferation and portal tract enlargement may help in differential diagnosis (Figure 12). Complications after duct-to-duct biliary reconstruction can be treated by dilation and internal stenting. With recurrent stenosis or persistent postoperative leak, Roux-en-Y choledochojejunostomy is the preferred treatment. In small children and in all patients transplanted for biliary atresia or with a partial graft, Roux-en-Y choledochojejunostomy is the reconstruction method of choice. In these patients,

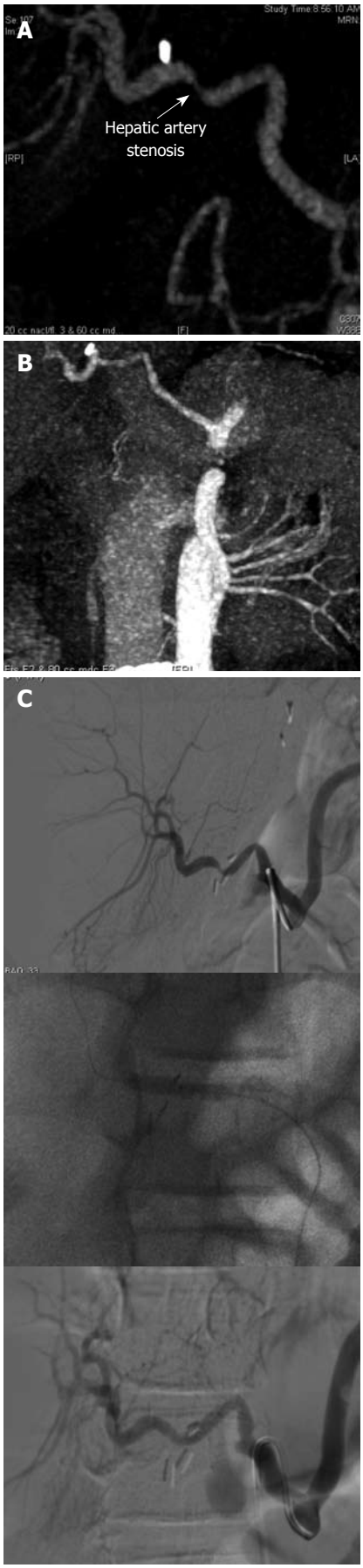

Figure 9 A case of hepatic artery stenosis. Reconstructed computed tomographic angiography demonstrating severe hepatic artery stenosis in an extended right graft recipient (A), and complete resolution of the stenosis 6 mo later (B), after stenosis treatment by early interventionally guided balloon angioplasty (C).

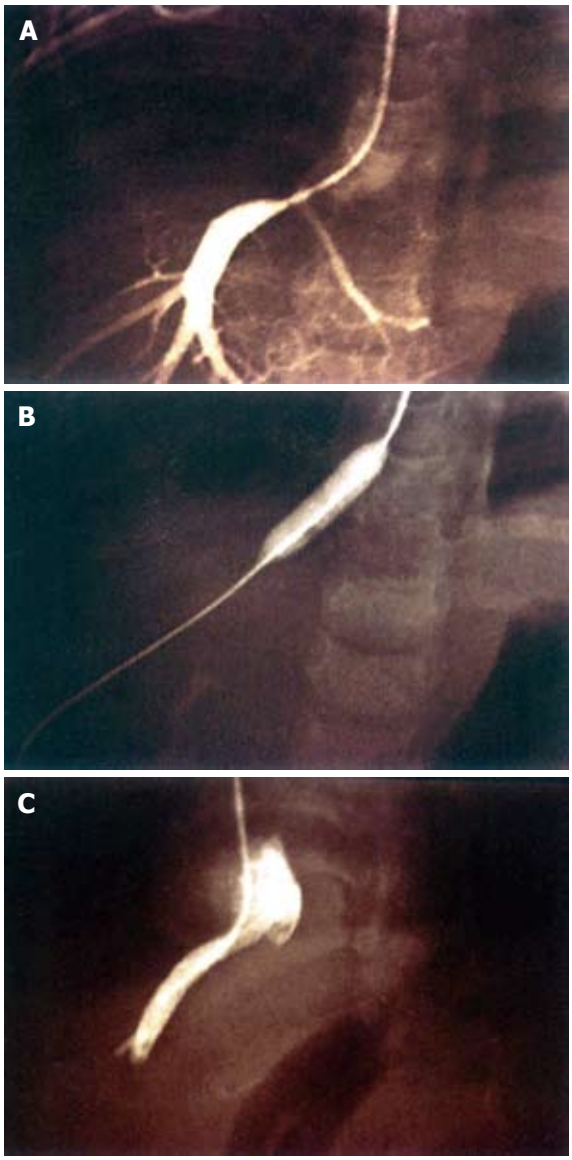

Figure 10 Venogram of hepatic venous outflow obstruction after left lateral segment split-liver transplantation. Venogram demonstrates a stenosis at the left hepatic vein anastomosis (A). Balloon angioplasty is performed (B), with resolution of the stenosis (C).

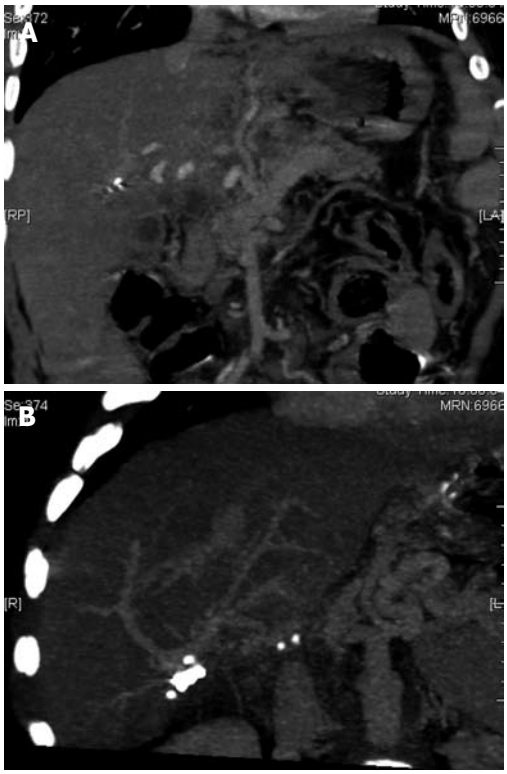

Figure 11 Portal vein thrombosis. Computed tomographic angiography with evidence of portal vein thrombosis and cavernomatous degeneration with collateral drainage through the left gastric vein (A), and evidence of intrahepatic portal flux restoration (B).

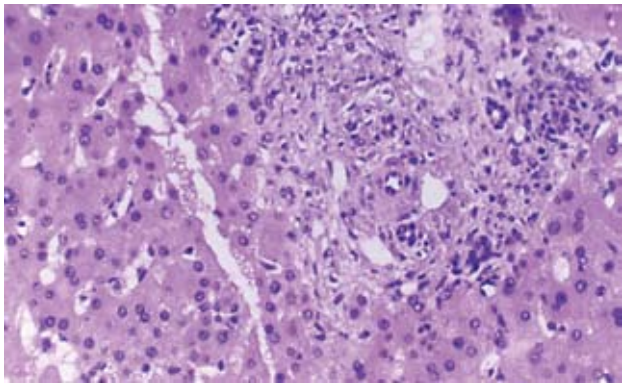

Figure 12 Liver biopsy performed in a left lateral segment recipient because of non-specifically elevated liver function tests. Histology shows biliary duct proliferation and portal tract enlargement suggestive of mechanic cholestasis.

dilatation and stenting are performed by percutaneous transhepatic cholangiography (Figure 13). The presence of multiple bile ducts has a documented increased risk for biliary complications[86].

Reoperation 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 secondary to multiple intra-abdominal adhesions, and sepsis. Infants and small children who have had only initial skin closure require secondary laparotomy for musculofascial closure in 5-7 d[87].

The overall incidence of re-transplantation ranges from 8% to 29%. The incidence of re-transplantation is similar for whole-organ allografts and partial allografts. The majority of re-transplantations result from acute allograft damage caused by either hepatic artery thrombosis or primary non-function; chronic rejection and biliary complications are uncommon causes. When re-transplantation for acute organ failure is undertaken in a timely manner, patient survival exceeds 80%. When re-transplantation is performed after prolonged immunosuppression for chronic allograft failure, often complicated by multiorgan insufficiency, the survival is only 50%.

Acute rejection

About 20%-50% of patients develop at least one episode of acute rejection in the first weeks after liver transplantation. The clinical picture of rejection

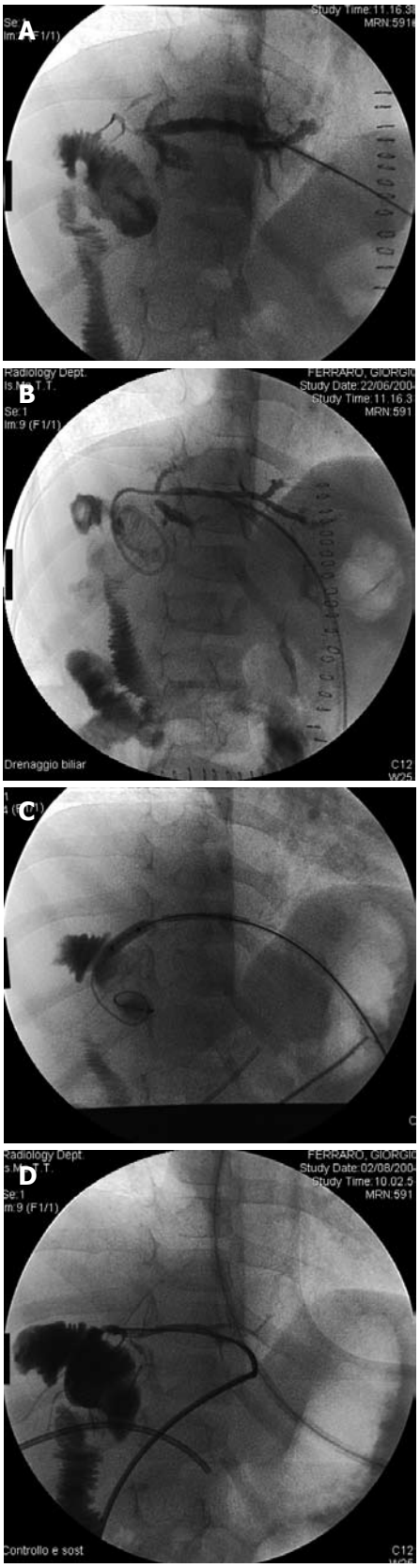

Figure 13 A case of biliary stenosis. Percutaneous transhepatic cholangiography performed in a left lateral segment recipient demonstrating intrahepatic biliary tree dilatation with stenosis of the hepaticojejunostomy (A), balloon bilioplasty (B), and transanastomotic percutaneous transhepatic biliary drainage positioning (C). Resolution of the stenosis after three sessions of bilioplasty (D).

includes fever, irritability, malaise, leucocytosis, often with eosinophilia, and increased γ-GT, bilirubin,

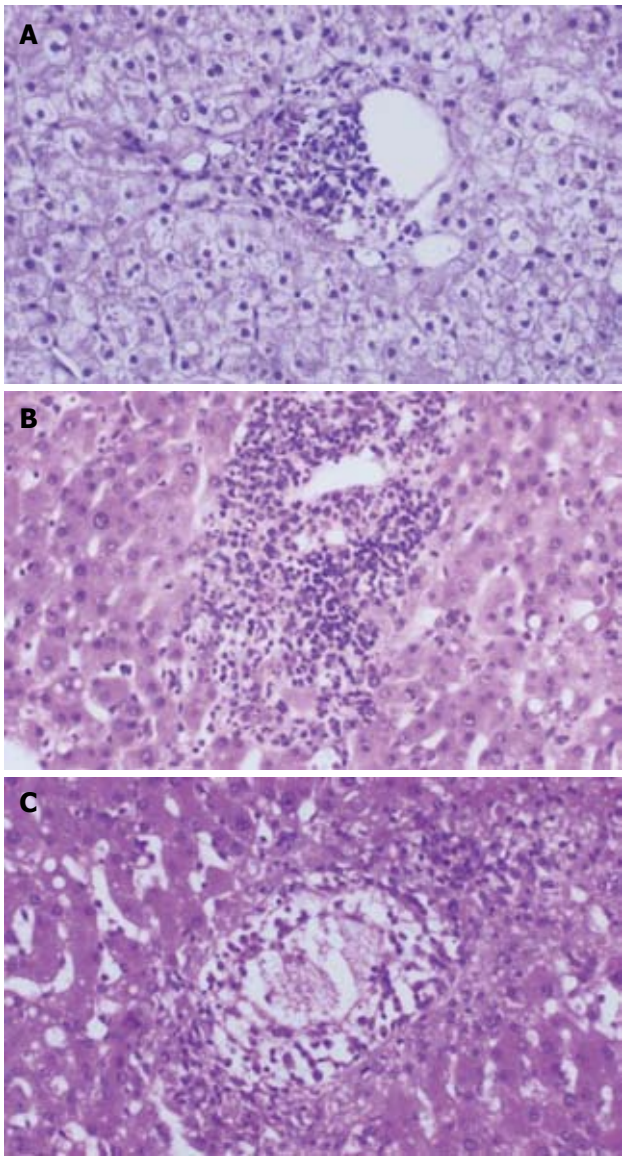

Figure 14 Acute cellular rejection: histopathological findings and grading. A: Mild acute cellular rejection, portal tracts are mildly expanded because of a predominantly mononuclear, but mixed portal inflammation. Rejection infiltrate is composed of blastic and small lymphocytes, eosinophils, macrophages, and occasional plasma cells. Lymphocytes are also present inside the basement membrane of the small bile ducts and in the subendothelial space of small portal vein branches. B: Moderate acute cellular rejection, all the portal tracts are markedly expanded by a predominantly mononuclear, but mixed inflammation. Centrilobular inflammation and hepatocyte necrosis and dropout are absent. C: evere acute cellular rejection, severe expansion of the portal tracts because of inflammation with focal portal-to-portal bridging; perivenular inflammation with hepatocyte necrosis and dropout; inflammation and damage to small bile ducts.

and transaminases. A liver biopsy is required to confirm rejection. Acute rejection is characterized by the histological triad of endothelialitis, portal triad lymphocyte infiltration with bile duct injury, and hepatic parenchymal cell damage[88] (Figure 14). Severity of acute rejection is scored according to the Banff scheme, which includes the descriptive grades indeterminate, mild, moderate, and severe, and a semi-quantitative rejection activity index (RAI) scoring on a scale from 0 to 3 the prevalence and severity of portal inflammation, bile duct damage, and subendothelial inflammation[89] (Tables 5

Table 5 Banff grading of acute liver allograft rejection

Assessment	Criteria	RAI
Indeterminate	Portal inflammatory infiltrate that fails to meet criteria for the diagnosis of acute rejection	1-2
Mild	Rejection infiltrate in a minority of the triads that is generally mild and confined within the portal spaces	3-4
Moderate	Rejection infiltrate expanding most or all of the triads	5-6
Severe	As above for moderate, with spillover into the periportal areas and moderate to severe perivenular inflammation that extends into the hepatic perenchyma and is associated with perivenular hepatocyte necrosis	> 6

Table 6 Rejection activity index (RAI)

Category	Criteria	Score
Portal inflammation	Mostly lymphocytic inflammation involving, but not noticeably expanding, a minority of the triads	1
	Expansion of most or all of the triads by a mixed infiltrate containing lymphocytes with occasional blasts, neutrophils, and eosinophils	2
	Marked expansion of most or all of the triads by a mixed infiltrate containing numerous blasts and eosinophils with inflammatory spillover into the periportal parenchyma	3
Bile duct inflammation damage	A minority of the ducts are cuffed and infiltrated by inflammatory cells and show only mild reactive changes such as an increased nuclear-to-cytoplasmatic ratio of the epithelial cells	1
	Most or all of the ducts infiltrated by inflammatory cells. More than an occasional duct shows degenerative changes such as nuclear pleomorphism, disordered polarity, and cytoplasmatic vacuolization of the epithelium	2
	As above for the 2nd criterion, with most or all of the ducts showing degenerative changes or focal luminal disruption	3
Venous endothelial inflammation	Subendothelial lymphocytic infiltration involving some, but not a majority, of the portal and/or hepatic venules	1
	Subendothelial infiltration involving most or all of the portal and/or hepatic venules	2
	As above for the 2nd criterion, with moderate or severe perivenular inflammation that extends into the perivenular parenchyma and is associated with perivenular hepatocyte necrosis	3

and 6).

The primary treatment of rejection is a short course of high-dose steroids. Bolus doses administered over a 3-6-day period with a rapid taper to baseline therapy are successful in the majority of cases. When refractory or recurrent rejection occurs, conversion from cyclosporine to tacrolimus, or antilymphocyte therapy using the monoclonal antibody, ornithine-ketoacid transaminase orthoclone, have been successfully used[90,91].

INFECTIONS

Immunosuppressive drugs used to prevent rejection inhibit activation of T lymphocytes, medullar cell proliferation and macrophage function, therefore creating an optimal environment for the development of infections. Infectious complications now represent the most common source of morbidity and mortality after transplantation.

Bacterial infections occur in the immediate post-transplantation period and are most often caused by Gram-negative enteric organisms, enterococci, or staphylococci. Sepsis originating at sites of invasive monitoring lines can be minimized by replacing or removing all of the intraoperative lines soon after transplantation. The use of prophylactic antibacterial antibiotics is discontinued as soon as possible to avoid the development of resistant organisms.

Fungal infection is a potential problem in the early post-transplantation period. To prevent fungal infection, aggressive protocols for pre-transplantation prophylaxis have been proposed[92]. Fungal infection most often occurs in high-risk patients requiring multiple operative procedures, re-transplantation, hemodialysis or continuous hemofiltration, pre-transplant chemotherapy, and multiple antibiotic courses. The authors use antifungal postoperative prophylaxis with liposomal amphotericin B only in high-risk patients undergoing liver transplantation.

Early and severe viral infections are caused by viruses of the herpes family, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex virus[93]. The risk of developing either CMV or EBV infection is influenced by the preoperative serological status of the transplant donor and recipient[94,95]. Seronegative recipients receiving seropositive donor organs are at greatest risk. Various prophylactic protocols, including intravenous IgG and hyperimmune anti-CMV IgG, associated with acyclovir or ganciclovir have been used to decrease the incidence of symptomatic CMV and EBV infection, although seroconversion in naive recipients inevitably occurs[94,96]. The suspicion of CMV infection is suggested by the presence of fever, leukopenia, maculopapular rash and hepatocellular abnormalities, respiratory insufficiency, or gastrointestinal hemorrhage. Hepatic biopsy or endoscopic biopsy of colonic or gastroduodenal sites allows early diagnosis with immunohistochemical recognition. Nowadays, the availability of specific antiviral drugs like ganciclovir, foscarnet and more recently valaciclovir, have radically modified the prognosis of CMV infection. At the start of the 1990s, the concept of pre-symptomatic therapy

was introduced as a strategy to prevent the incidence of CMV-related disease, based on the principle of not administering antiviral medications up to the point when these will have maximum effect, and monitoring CMV antigenemia (pp65) or viremia (CMV DNA)[97,98].

Herpes simplex virus infections, similar to those seen in non-transplant patients, require treatment with acyclovir when diagnosed.

EBV infection represents a potential risk for the pediatric transplant recipient. EBV infection has a variable clinical picture including a mononucleosis-like syndrome, hepatitis-simulating rejection, extranodal lymphoproliferative infiltration, peritonsillar or lymph node enlargement, or encephalopathy. Monitoring of EBV blood viral load by quantitative polymerase chain reaction (PCR) is the best predictor of risk. When evidence of active infection exists, an acute reduction in immunosuppression is mandatory. The authors recommend monthly EBV-DNA PCR counts and more frequent monitoring in case of increasing viral load levels. As a result of the lack of a standardized EBV DNA count methodology, no common cutoff exists. In the authors' experience, more than 500 genomes/10^5 peripheral blood leukocytes identify patients who benefit from reduction in primary immunosuppression[99]. Antiviral therapy with ganciclovir and CMV-IgG is also used, although no definitive data support their use[100,101].

Other post-transplantation infectious complications include adenovirus hepatitis, varicella, and enterovirus-induced gastroenteritis. *Pneumocystis carinii* infection has been nearly eliminated by the prophylactic administration of sulfisoxazole and trimethoprim or aerosolized pentamidine.

MANAGING IMMUNOSUPPRESSIVE THERAPY

The immune system recognizes the graft as foreign and begins a destructive immune response mediated principally by the T lymphocytes. In order to avoid destruction of the graft, immunosuppressive drugs must be administered. Progress in transplant surgery in the last 20 years has been characterized in large part by the introduction of calcineurin inhibitors that today represent the keystone of most immunosuppressive protocols[102,103]. In the last decade, new drugs that selectively target various cellular activation pathways have been proposed and used. The following are the most commonly used drugs in pediatric liver recipients.

Corticosteroids

Corticosteroids were the first drugs to be used to control rejection and are still an essential element of the immunosuppressive regimen; they are effective in both the prevention and treatment of graft rejection. They act through intracellular receptors expressed in all cells of the body. Their immunosuppressive action mechanism, not fully clarified yet, is linked to the suppression of antibody production; inhibition of synthesis of cytokines such as interleukin-2 (IL-2) and interferon-γ; reduction in the proliferation of helper and suppressor T cells, cytotoxic T cells, and B cells; and the migration and activity of neutrophils.

Long-term clinical experience with steroid use has documented a host of adverse effects. Over-immunosuppression is associated with increased incidence of bacterial, fungal and viral infections. In addition, patients taking steroids carry an increased risk for developing malignancies, especially lymphomas and skin cancers[104]. Detrimental metabolic effects of steroids are wide ranging and are of particular concern for the pediatric transplant patient[105-107]. In terms of hospital costs, the calculated 10-year cumulative expense for steroid-related complications in adult kidney recipients has been shown to be 5300 $ per patient per year[108]. Efforts are underway to develop immunotherapy regimens in which steroids can be withdrawn early, or not used at all.

The experience of steroid weaning after pediatric liver transplantation was summarized in 2000 by Reding[109]. There are a total of nine recent studies, not all of which were non-randomized and uncontrolled. Steroid treatment could be successfully stopped in 21%-100% of the transplanted patients. The risk of rejection was not significantly increased, and varied from 7% to 29%. Chronic rejection did not seem to be increased[110-118] (Table 7). The conclusions of this review are the following: (1) weaning of steroids after pediatric liver transplanatation is safe and, most of the time, beneficial; and (2) in many patients, calcineurin inhibitor monotherapy can be achieved, suggesting that the next step could be the adoption of steroid-free immunosuppressive protocols.

In a non-randomized study, Reding *et al*[119] compared pediatric liver transplantation under steroid-free immunosuppression in children who received combined tacrolimus and antibody to the IL-2 receptor of T cells (basiliximab), with matched historical recipients taking tacrolimus and steroids. Twelve-month rejection-free survival was similar in the steroid-free group compared with the corticosteroid group. The authors performed the first prospective, controlled, randomized study designed for children undergoing liver transplantation to test the possibility of avoiding the use of corticosteroids under baseline tacrolimus immunosuppression plus basiliximab induction, which confirmed no harmful effect of steroid avoidance on graft acceptance[120].

Corticosteroid withdrawal or avoidance can be difficult in patients with autoimmune hepatitis, primary biliary cirrhosis, or primary sclerosing cholangitis. In these patients it might be desirable to include steroids in the immunosuppressive protocol as a principle, although definitive and convincing data are not available.

Calcineurin inhibitors

Cyclosporine and tacrolimus are classified as calcineurin inhibitors because they inhibit T-cell responses and bind to intracellular proteins called immunophilins.

Table 7 Literature review of immunosuppressive protocol with steroid weaning after pediatric liver transplantation

Author	Year	Patients (*n*)	Protocol	Weaning (%)		Graft loss	Rejection (%)	
				Performed	Success		Acute	Chronic
Margarit *et al*[110]	1989	18	CsA+Aza	83	61	13%	27	13
Andrews *et al*[111]	1994	119	CsA+Aza[1]	44	67	No	13	No
Dunn *et al*[112]	1994	73	CsA+Aza	51	76	4%	7	4
McDiarmid *et al*[113]	1995	13	CsA+Aza			No	No	No
McKee *et al*[114]	1997	29	TAC	83	71		29	
Martin *et al*[115]	1998	55	CsA+Aza	44	76	No	11	No
Reding *et al*[109,116]	2000	375	CsA (*n* = 23)		21	No	No	No
			CsA-ME (*n* = 24)			No	No	No
			TAC (*n* = 31)			No	10	No
Atkison *et al*[117]	2002	94	CsA+Aza[2]	71	91		21	
Toyoki *et al*[118]	2004	8	TAC	100	100	No	13	No

CsA: Cyclosporine; CsA-ME: Cyclosporine microemulsion; Aza: Azathioprine; TAC: Tacrolimus. [1]In 53% of the weaned children; [2]Some patients received antilymphocyte globulin or OKT3 induction.

The immunophilin-drug complex competitively binds to and inhibits the phosphatase activity of calcineurin. Calcineurin inhibition indirectly blocks the transcription of cytokines, particularly IL-2, which regulate the proliferative T-cell response[121]. Calcineurin inhibitors have similar side-effect profiles, which include dose-dependent nephrotoxicity, neurotoxicity, and hypertension. Most adverse effects are reversible after dose reduction or discontinuation of the drug[122,123]. Tacrolimus has not been associated with cosmetic adverse effects such as hypertrichosis and gingival hyperplasia observed in cyclosporine-immunosuppressed children. Moreover, tacrolimus is associated with less hyperlipidemia and a lower adverse cardiovascular risk profile than cyclosporine[124], but with slightly more *de novo* diabetes and gastrointestinal symptoms[125]. In some studies, tacrolimus has been described to cause a higher incidence of post-transplant lymphoproliferative disease[126,127], but this has not been confirmed in other authors' experiences[128]. Hypertrophic cardiomyopathy has been reported with prolonged use of tacrolimus at unusually high levels[129].

Calcineurin inhibitors are mainly absorbed from the small intestine and are metabolized in the liver and small intestine by the cytochrome P4503A enzyme system[130]. The majority of their metabolites are excreted in bile[131]. The most important interactions are with enzymes or drugs that induce or inhibit the cytochrome P4053A, which results in reduced or increased calcineurin inhibitors levels.

Tacrolimus or cyclosporine usually represents the primary drug of most immunosuppressive regimens. Over the last 10 years, the use of tacrolimus has increased, being nowadays preferred to cyclosporine[132]. Tacrolimus and cyclosporine have been compared in large multicenter trials that showed similar 1-year patient and graft survival, with a significantly reduced incidence of acute rejection as well as steroid-resistant rejection in children treated with tacrolimus. Moreover, tacrolimus is superior to cyclosporine for the treatment of rejection episodes that may resolve when patients are switched from cyclosporine to tacrolimus therapy[97,133].

Table 8 Desired trough concentrations of calcineurin inhibitors after pediatric liver transplantation

Time post-transplant (mo)	Target level (mg/L)	
	Cyclosporine	Tacrolimus
0-3	200-250	10-15
4-12	150-200	8-10
> 12	50-100	5-8

Cyclosporine: The microemulsion form of cyclosporine, Neoral, is the formulation mainly used, which has replaced the original formulation Sandimmune because of its greater and more consistent bioavailability. Pharmacokinetics features of cyclosporine that are to be considered in children are the following: (1) cyclosporine bioavailability correlates with age, being lower in younger patients; and (2) cyclosporine is metabolized in children at a higher rate than adults, and appears to be inversely related to age[134]. The type of biliary anastomosis (e.g. Roux-en-Y biliary anastomosis for biliary atresia) and concomitant disease (e.g. cystic fibrosis) may affect absorption and bioavailability[135,136]. The recommended starting dose of Neoral is 5 mg/kg twice daily, which should be administered orally within the first 12 h of abdominal closure. Intravenous cyclosporine can be administered at a dose of 2 mg/kg per day in two divided doses by continuous infusion over 2-6 h in case of poor absorption or inadequate trough concentrations. After the first administration, the dose is adjusted in order to keep trough concentrations within a recommended target range (Table 8). Trough levels are poor predictors of rejection episodes or outcome of graft recipients[137], therefore, drug concentration in blood drawn 2 h post-dose has been proposed recently to be a superior estimate of the subsequent 12 h cyclosporine exposure[138,139].

Tacrolimus: The recommended tacrolimus starting dose is 0.05-0.1 mg/kg, administered orally within the first 12 h after abdominal closure. Subsequently, doses are adjusted in order to maintain trough concentrations

Table 9 Use of sirolimus in primary immunosuppressive regimens in liver transplantation

Author	Immunosuppression	No. of patients	Survival (%)		Acute rejection (%)	Follow-up (mo)
			Patient	Graft		
McAlister *et al*[153]	TRL, SRL, STER[1]	32	92		3	8
McAlister *et al*[154]	TRL, SRL, STER[1]	56	93	91	14	23
Peltekian *et al*[155]	TRL, SRL, STER[1]	42	93	90	10	14
Pridöhl *et al*[156]	TRL, SRL, STER	22	91	78	14	14
Sindhi *et al*[157]	TRL, early SRL, STER	6			17	15
	TRL, late SRL, ATG	9			33[2]	3

ATG: Antithymoglobulin; SRL: Sirolimus; STER: Corticosteroids; TRL: Tacrolimus; [1]Corticosteroids withdrawal 3 mo after transplantation; [2]Rejection episodes observed before sirolimus was introduced in the immunosuppressive regimen.

within a recommended target range (Table 8). The trough level is widely accepted for routine tacrolimus drug level monitoring. Large inter- and intra-individual differences in pharmacokinetics exist. The elimination half-life of tacrolimus in children is 50% of that in adults, and clearance is correspondingly two to four times faster[140,141]. Therefore, children require higher doses to achieve similar tacrolimus concentrations.

Mycophenolate mofetil

The active metabolite of mycophenolate mofetil, mycophenolic acid, is a selective inhibitor of the enzyme inosine monophosphate dehydrogenase, which is essential for the *de novo* pathway of purine synthesis[142]. Inhibition of the *de novo* pathway results in the depletion of guanosine nucleotides and arrested lymphocytes replication because they are unable to use the alternative pathway for nucleotide production[143].

Mycophenolate mofetil has been used successfully as an alternative immunosuppressive agent in patients with chronic rejection, refractory rejection, or severe calcineurin inhibitor toxicity[144,145]. Mycophenolate mofetil has also been used in calcineurin-inhibitor and corticosteroid-sparing immunosuppressive protocols, without increasing the risk of rejection[146,147]. The suggested dose for pediatric liver transplant recipients is 15 mg/kg twice daily[148]. Pharmacokinetic studies showed large inter-individual variations in mycophenolic acid parameters[149,150], which indicates the need for therapeutic drug monitoring and individualized dosing. The most relevant adverse effects of mycophenolate mofetil are dose-dependent gastrointestinal symptoms and bone marrow suppression[147,151]. Acyclovir and ganciclovir increase mycophenolic acid efficacy, whereas cholestyramine, oral antibiotics, antacids, cyclosporine, and high tacrolimus concentrations reduce its concentration[148-150].

Sirolimus

Sirolimus (rapamycin) is a macrolide antibiotic with potent immunosuppressive properties that acts by blocking T-cell activation by way of IL-2R post-receptor signal transduction[152]. Sirolimus has been used in small, uncontrolled studies in liver transplant recipients (Table 9) and reduces rate of acute rejection, when used in combination with calcineurin inhibitors, even at low doses, or facilitates early steroid withdrawal, while maintaining low rates of acute rejection[153-157].

Sirolimus has also been used as rescue treatment in chronic rejection and calcineurin inhibitor toxicity[157-159], whereas attempts to use sirolimus as a single primary immunosuppressive agent have resulted in a high rate of acute rejection[160]. Sirolimus has not yet been approved by the US Food and Drug Administration for use in liver transplantation. One trial to evaluate sirolimus in liver transplant recipients was halted because of an increased incidence of hepatic artery thrombosis. In contrast, other studies have not confirmed this finding[154,161,162], and a possible benefit of sirolimus in the prevention of coronary artery restenosis after percutaneous coronary revascularization has been described[163]. Sirolimus has shown antineoplastic activity, inhibiting angiogenesis in malignant tissue through reduction of vascular endothelial growth factor secretion, which may provide a specific indication for using of the drug in patients transplanted for primary liver malignancy[164].

Sirolimus drug interactions are similar to those of calcineurin inhibitors. It has a long half-life (40-86 h) and intra- and inter-individual variation[152,165]. Therefore, daily sirolimus monitoring is not necessary and monitoring trough level twice weekly for the first month and weekly for the next month is recommended, targeting a 5-15 mg/L range. Sirolimus levels increase during simultaneous administration of cyclosporine[166]. The most relevant dose-related side effects of sirolimus are hyperlipidemia, thrombocytopenia and leukopenia[153,157].

IL-2 receptor antibodies

T cells involved in acute rejection act by exposing activation markers such as the IL-2 receptors. Therefore, anti-IL-2 receptor therapy appears to be a promising option for specific immunosuppression. IL-2 receptor antibodies have been used primarily in children as induction agents in double or triple immunosuppression protocols. Preliminary experience in pediatric liver recipients is encouraging: pooled data from the available papers from the literature encompassed 79 patients treated with daclizumab, 165 with basiliximab, and 209 no-induction controls; incidence of acute rejection was lower in the induction groups[119,120,167-172] (Table 10).

A multicenter trial studied basiliximab pharmacokinetics and pharmacodynamics in children. It demonstrated that to achieve efficacious results, pediatric patients less than 35 kg in weight should receive two intravenous 10-mg

Table 10 Use of IL-2 receptor antibodies in primary immunosuppressive regimens in pediatric liver transplantation

Author	Immunosuppression	No. of patients	Survival (%)		Acute rejection (%)	Follow-up (mo)
			Patient	Graft		
Asensio *et al*[167]	TRL, STER	21	80	80	63	12
	TRL, STER, BAS	34	80	80	30	
Strassburg *et al*[168]	TRL, STER	12			42	28
	CSA, STER, AZA	9			66	
	CSA, STER	12			42	
	CSA, STER, BAS	21			33	
Heffron *et al*[169]	TRL, MMF, STER	20	85	88	50	24
	TRL,[2] MMF, DAC, STER	61	93	73	15	
Reding *et al*[119]	TRL, STER	20			50	12
	TRL, BAS, MMF[1]	20			25	
Ganschow *et al*[170,171]	CSA, STER	54	94		54	28-52
	CSA, STER, BAS	54	98		17	
Schuller *et al*[172]	TRL, MMF, STER	12			66	14
	TRL, MMF, DAC, STER	18			0	6
Spada *et al*[120]	TRL, STER	36	91	86	32	24
	TRL, BAS	36	87	80	12	

CSA: Cyclosporine; DAC: Daclizumab. [1]Mycophenolate mofetil was given in the first 9 patients. [2]Tacrolimus was given starting from postoperative day 7.

doses, and those weighing ⩾ 35 kg should receive two 20-mg doses of basiliximab. The first dose should be given within 6 h after organ reperfusion, and the second on day 4 after transplantation. A supplemental dose may be considered for patients with a large volume of drained ascitic fluid relative to body size[173]. For daclizumab, various different dosing regimens have been used[169,174]. A dual regimen of 1 mg/kg on days 0 and 4 provides receptor saturation for up to 21 d.

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLDS)

PTLDs are a heterogeneous group of diseases, ranging from benign lymphatic hyperplasia to lymphomas. PTLD is the most frequent tumor in children following transplantation, and occurs in the majority of the cases within the first 2 years after transplantation[175]. Late forms have usually an aggressive clinical course and severe prognosis. The development of PTLD in pediatric liver transplant recipients is favored by the intensity of the immunosuppression, its lifetime duration, and the absence of prior exposure to EBV infection in 60%-80% of patients. Risk factors for PTLD development are: (1) high total immunosuppression load; (2) EBV-naive recipients; and (3) the intensity of active viral load[176,177]. No single immunosuppressive agent has been directly related to PTLD. An important pathogenic feature favoring PTLD development is EBV infection.

Treatment of PTLD is based on the immunological cell typing and clinical presentation. Documented PTLD requires an immediate decrease or withdrawal of immunosuppression, taking into account the increased risk of organ rejection[100,101]. If a tumor expresses the B-cell marker CD20, the anti-CD20 monoclonal antibody rituximab has been successfully used. In some studies, the combination of cyclophosphamide, prednisone and rituximab has shown a response rate of 100%, with minimal toxicity[178,179]. Patients who have aggressive monoclonal malignancies have poor prognosis even with immunosuppressive reduction, acyclovir, surgery, and conventional chemotherapy or radiation therapy. Recently, autologous EBV-specific cytotoxic T-lymphocytes have proved effective in enhancing EBV-specific immune responses and reducing viral load in organ transplant recipients with active infection, and have been successfully used as first-line treatment of EBV-related PTLD[180].

LATE LIVER ALLOGRAFT DYSFUNCTION

There are several potential causes of late liver allograft dysfunction and differential diagnosis can be difficult because of overlapping clinical, serological and histopathological features. Recurrence of the native liver diseases after transplantation is a less significant problem in the pediatric population in comparison to adults. Recurrent infections and immune-based diseases are the most difficult diagnostic challenges. Most late causes of liver allograft dysfunction are detected because of abnormalities in routinely monitored liver tests; clinical signs and symptoms are much less common. When signs or symptoms do occur, liver biopsy is indicated. Common causes of late dysfunction in the pediatric population are shown in Table 11.

Late-onset acute rejection

Late-onset acute rejection may show slightly different features than typical acute rejection episodes seen early after transplantation, and is commonly characterized by: (1) predominantly mononuclear portal inflammation; (2) venous subendothelial inflammation of portal or central veins or perivenular inflammation; and (3) bile duct inflammation and damage. Late-onset acute rejection can

Table 11 Common causes of late dysfunction in the pediatric population

	Incidence at 5 yr (%)	Risk factors
Acute rejection	Variable (< 30)	Inadequate immunosuppression Treatment with immune activating drugs (e.g. interferon) History of autoimmune liver disease
Chronic rejection	-3	Inadequate immunosuppression Treatment with immune-activating drugs (e.g. interferon) Refractory acute rejection Chronic rejection in a previous failed allograft
Recurrent AIH	-30	Suboptimal immunosuppression AIH type I Severe inflammation in native liver HLA DR3 or DR4
De novo AIH	< 5	
Recurrent PBC	20-30	Tacrolimus as baseline immunosuppression Living-related donor Steroid and other immunosuppression withdrawal
Recurrent PSC	20-30	Male sex; donor-recipient gender mismatch Intact colon at time of transplantation
Idiopathic post-transplant hepatitis	5-60	

AIH: Autoimmune hepatitis; PBC: Primary biliary cirrhosis; PSC: Primary sclerosing cholangitis.

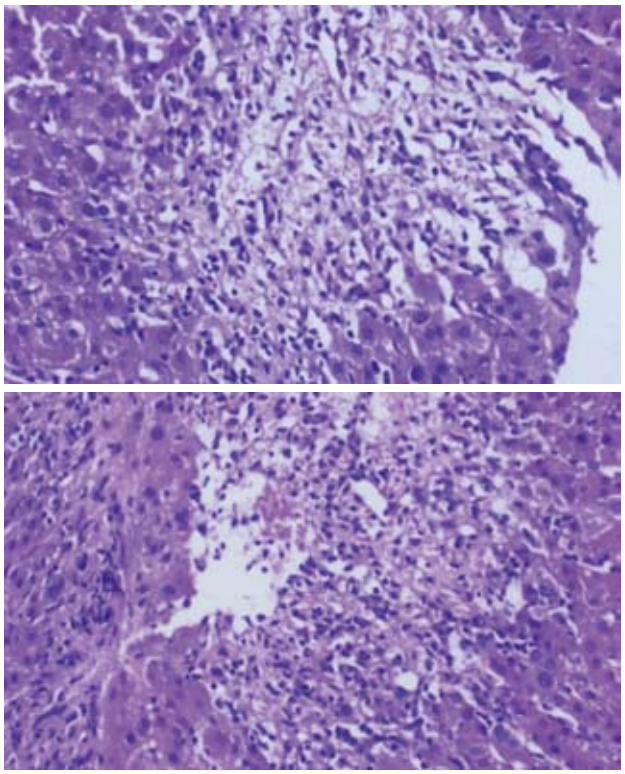

Figure 15 Histological findings in chronic rejection: Little portal inflammation in conjunction with bile duct loss affecting > 50% of the portal tracts and moderate or severe perivenular fibrosis.

also manifest as so-called central perivenulitis [181-183], or may resemble chronic hepatitis[184,185]. Mild cases may resolve spontaneously[183], but more severe forms warrant more aggressive treatment.

Chronic rejection

Chronic rejection develops in 5%-10% of transplanted patients. The primary clinical manifestation is progressive cholestasis. This course can occur within weeks from transplantation or later, and can be asymptomatic or follow persistent and/or unresponsive acute rejection and/or inadequate immunosuppression. Two clinical forms have been described[186]. In the first, named vanishing bile duct syndrome, the biliary epithelium is primarily injured with changes ranging from senescence (early stage) to severe ductopenia in at least 50% of the portal tracts (late stage)[187]. This form can be successfully treated by conversion from cyclosporine to tacrolimus immunosuppression protocols. Re-transplantation is necessary in non-responding children. The second subtype is characterized by the development of progressive ischemic injury to bile ducts and hepatocytes, which causes ductopenia and ischemic necrosis with fibrosis (Figure 15). In this setting, the diagnosis is rarely based on histology alone, because arteries with pathognomonic changes are rarely present in needle biopsy specimens. Bile duct injury and ductopenia, however, can be caused by biliary strictures, hepatic artery pathology, adverse drug reactions, and CMV. Selective hepatic angiography showing pruning of the intrahepatic arteries with poor peripheral filling and segmental narrowing supports a diagnosis of chronic rejection[188,189]. This form nearly always requires retransplantation.

Recurrent and new-onset or de novo autoimmune hepatitis

Theoretically all forms of autoimmune hepatitis after transplantation can be classified as rejection[190-192]. No conventional clinical tests differentiate an autoimmune response from rejection. The diagnosis of autoimmune hepatitis is established by a combination of serological, molecular biological and histopathological findings. Non-organ-specific autoantibodies are a requisite for the diagnosis, and they typically include smooth muscle antibodies (SMAs), antinuclear antibodies (ANAs), and antibodies to liver kidney microsome (anti-LKM)[193]. Minimal diagnostic criteria for recurrent or *de novo* au-

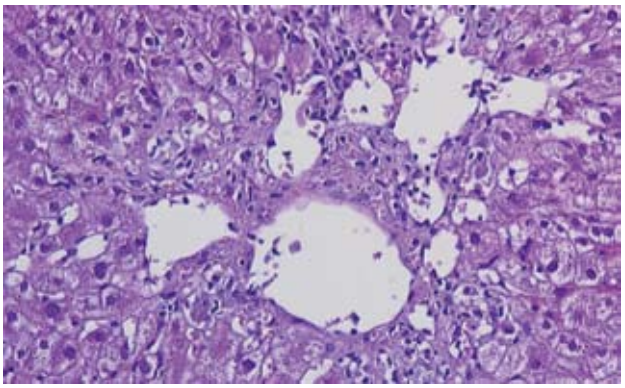

Figure 16 Histological appearance of recurrent or new-onset autoimmune hepatitis characterized by moderate portal inflammation, prominent interface activity, relative sparing of the bile ducts, and perivenular accumulation of inflammation.

toimmune hepatitis in an allograft are: (1) interface hepatitis with portal lymphocytic infiltrates (Figure 16); (2) presence of ANA, SMA or anti-LKM; (3) hypergammaglobulinemia; and (4) exclusion of virus-induced or drug-related hepatitis and late acute or chronic rejection. Most adult recipients respond to an increase in immunosuppression, whereas pediatric recipients often require the use of second-line immunosuppressive drugs (azathioprine, mycophenolate mofetil). A cautious approach to withdrawal of immunosuppression is warranted in all patients transplanted for autoimmune hepatitis, and the consequences of recurrent disease within the graft will require prolonged follow-up. A recent study, evaluating protocol liver biopsies performed in asymptomatic children 1, 5 and 10 years after transplantation, documented that chronic hepatitis is a common finding in children after liver transplantation, and is associated with a high risk of developing progressive fibrosis, which leads to cirrhosis, and with the presence of autoantibodies[194].

Idiopathic post-transplant hepatitis

Chronic hepatitis that cannot be ascribed to a particular cause is defined as idiopathic post-transplant hepatitis. Cases presenting with central perivenulitis probably represent centrilobular-based acute rejection or autoimmune hepatitis, if autoantibodies are also present[185], because allograft dysfunction usually responds to increased immunosuppression[185,195]. Some cases may represent a form of rejection with features of chronic hepatitis[195]. A diagnosis of idiopathic post-transplant hepatitis does not usually require treatment with increased immunosuppression. However, as some cases do show progressive fibrosis, the management of those with moderate to marked activity needs to be clarified.

Primary sclerosing cholangitis

Recurrent primary sclerosing cholangitis is nearly identical to that seen in native livers[196,197]. Most patients with suspected recurrent disease are asymptomatic after transplantation. An accurate diagnosis of primary sclerosing cholangitis recurrence requires well-defined cholangiographic and histological criteria. Other disorders that can produce biliary strictures after transplantation should be excluded. Graft with primary sclerosing cholangitis recurrence shows biliary strictures, acute and chronic pericholangitis, and centrilobular hepatocanalicular cholestasis periductal fibrosis[198].

Table 12 UNOS pediatric liver Kaplan-Meier patient and graft survival rates for transplants performed between 1997 and 2004

Recipient age (yr)	Patient survival (yr)			Graft survival (yr)		
	1	3	5	1	3	5
< 1	89	82	78	81	70	63
1-5	86	80	77	78	71	67
6-10	91	86	86	84	76	75
11-17	93	87	81	87	77	67

One-year survival based on 2002-2004 transplants, 3-year survival based on 1999-2002 transplants, 5-year survival based on 1997-2000 transplants.

OUTCOME FOLLOWING TRANSPLANTATION

The overall results following liver transplantation are rewarding. The European Liver Transplantation Registry (ELTR) reports liver transplantation activity in Europe, and represents 5895 children transplanted between 1988 and 2005. Overall 1-year patient and graft survival was 84% and 73%, respectively, in patients older than 2 years at the time of transplantation, and 81% and 71%, respectively, in children < 2 years of age. Ten-year patient and graft survival rates for the same age groups were 75% and 61%, and 74% and 60%, respectively. Similarly, UNOS reported survival rates of the 9064 pediatric patients transplanted between 1997 and 2004. One-, 3- and 5-year patient and graft survival rates stratified according to recipient age at the time of transplant are reported in Table 12. Overall 1-year patient and allograft survival reported to the Studies of Pediatric Liver Transplantation (SPLIT) registry, representing 1611 patients, reached 88% and 82%, respectively, while these were 83% and 74%, respectively, 4 years after transplantation. Specific factors influencing early survival include age, diagnosis, severity of illness, and possibly allograft type[199].

Age

Survival for infants < 1 year of age or weighing < 10 kg has been reported to be between 65% and 80% overall, an improvement over the previously reported rates of 50%-60%[200]. Experienced programs have described even better patient survival rates at 3 mo[201]. Improved survival in these recipients results from technical innovations, better graft preparation and avoidance of life- and graft-threatening complications such as hepatic artery thrombosis and primary non-function.

Diagnosis

Survival after transplantation is similar in patients who have cholestatic and metabolic liver disease. Early survival rates are worse for patients who have acute liver failure[9,202,203] and liver tumors[11], but their long-term survival rates are similar to those of other recipients. Asso-

ciated multiorgan failure and a limited organ-acquisition time frame influence this result. Similar decreased survival trends are seen in patients who have a PELD score > 20, in status 1 recipients, and in patients whose PELD scores deteriorate significantly before transplantation[204].

Graft type

Donor factors influencing patient and graft survival include a donor age < 6 mo or > 50 years, even if some studies have demonstrated that elderly donors can be used safely[76]. The impact on the outcome of graft type (whole, reduced, split, or living-donor) is less clear. In the SPLIT registry, recipients of whole organs had better patient and graft survival than recipients of reduced, split, or living-donor allografts[205]. The US Scientific Registry of Transplant Patients database review has reported significantly lower risk of graft failure for patients aged < 2 years who received living-donor grafts compared to whole- and split-liver recipients. Older recipients showed a higher risk of graft loss and mortality after living-donor transplantation[206]. These conflicting results may have been influenced by the diverse experience accumulated in the transplant centers. Reports of whole-organ, living-donor, and split-liver outcomes from experienced centers showed no difference in patient and graft survival, and in biliary and vascular complications[53,60-62,207,208]. Successful transplantation of very small recipients with monosegments has been reported[209]. Overall, the best results can be achieved at centers that have extensive experience with all age groups and allograft types, allowing transplantation according to the needs of the recipient. The most important prognostic factor is the severity of the patient's illness at the time of transplantation[210]. The good survival rates obtained in patients receiving living-donor transplantation are positively influenced by the possibility to schedule transplantation before the development of life-threatening complications or severe malnutrition[211]. Children with acute liver failure, PELD > 20, and severe growth retardation have significantly lower overall survival than other groups. Previous major surgery influences the incidence of complications, especially bowel perforation, but do not negatively impact overall patient or graft survival. Long-term survival is mainly influenced by the consequences of prolonged immunosuppression such as infection, PTLD, renal insufficiency, hypertension, diabetes mellitus, and coronary artery disease[212].

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