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Received 5 February 1993.
Accepted 4 May 1993.

0041-1337/93/5606-1394$03.00/0
TRANSPLANTATION

Vol. 56, 1394–1398, No. 6, December 1993
Printed in U.S.A.

EPSTEIN-BARR VIRUS SEROLOGY AND EPSTEIN-BARR VIRUS-ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS IN PEDIATRIC LIVER TRANSPLANT RECIPIENTS

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Epstein-Barr virus serology was performed before and after transplantation in 116 patients of a total series of 261 pediatric OLT recipients. Thirty-nine percent had no immunity before OLT, but this percentage decreased to 11.2% at 6 months and 10.5% at 2 years after transplantation.

In this series, 10 children developed a B cell lymphoproliferative disease. Four had adenotonsillar involvement, 2 of them with associated digestive tract invasion. Three of these are alive, 2 after retransplantation for chronic rejection subsequent to arrest of immunosuppression. The fourth died from bone marrow aplasia. Three patients with multiorgan involvement died from multisystemic failure. The remaining 3 patients had a pseudotumoral mass. Two of these are alive, 1 after retransplantation for hepatic localization and secondary vascular and biliary complication. The last died from cachexia. Four patients developed the syndrome after viral reactivation, and 6 after primo infection. Four patients were under FK506 rescue therapy.

We conclude that a high rate of EBV primo infection is observed in the first months after transplantation. A significant percentage will develop EBV-associated lymphoproliferative disease, which causes death in half of the patients, including all these with multiorgan involvement. Half of the patients may survive, but because immunosuppression must be stopped, retransplantation for chronic rejection is often necessary in survivors.

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Viral infections and viral-related diseases are one of the main subjects of concern for physicians caring for transplanted children. Severe clinical expression of common viral pathogens may hamper the success of transplantation or even threaten the patient's life (*1–3*). Many procedures may help to reduce the incidence of these infections, such as vaccination before transplantation, use of blood derivatives from CMV-negative patients, regular infusions of hyperimmune plasma or immunoglobulin prophylaxis, systematic prophylaxis of herpetic infections with acyclovir, or even prophylactic treatment of patients at risk for CMV disease with ganciclovir (*4–7*). However, several viral pathogens remain insensitive to these prophylactic or therapeutic measures, such as adenovirus or Epstein-Barr virus (*2, 8*). This latter virus may not only cause acute mononucleosis, but is also likely to induce B lymphocyte proliferation in immunocompromised patients (*9–11*). This proliferation is favored by the loss of T cell-mediated control due to immunosuppression (*9–11*), and must be distinguished from true lymphoma, since spontaneous regression may be obtained after arrest of immunosuppression and T cell function recovery (*8, 12, 13*). Lowering of immunosuppression has recently been recommended as soon as the EBV EBER 1 gene is detected by in situ hybridization in liver tissue, because it may be an early marker of the disease (*13*). Serum IL-6 levels increase in these patients and may also be a marker of B cell proliferation (Prof. Fischer, personal communication, 1993). We report herein our experience of the EBV serology evolution in pediatric liver transplant recipients, and describe 10 patients of the series who developed an EBV-associated lymphoproliferative syndrome (LPS)*.

PATIENTS AND METHODS

Between March 1984 and April 1992, 261 children less than 15 years of age had an orthotopic liver transplantation performed at the Catholic University of Louvain, St. Luc Hospital. No patient among this series has been lost on follow-up.

General management has been detailed elsewhere (*5, 14*). Posttransplant immunosuppression included CsA (dose necessary to reach a whole blood specific trough level of 250 ng/ml in the immediate posttransplant period and 100–150 ng/ml at 1 year), AZA (1.5 mg/kg/day), and PRE (decreasing dosage to reach 0.5–1 mg/kg at day 7, 0.5-0.75 mg/kg at 1 month, 0.25–0.5 mg/kg/day at 3 months, 0.25 mg/kg/day at 6 months, and 0.5 mg/kg every other day from 6 months to 1 year [*5*]). In addition to this basal immunosuppression, several children have received antithymocyte globulins (Fresenius, Germany) or monoclonal antibodies (OKT3 antibody, Ortho Pharmaceutical Corp., Raritan, NJ; anti-IL-2 antibody, Lotact, Laboratory of Immunohematology, University of Louvain, Brussels) as part of protocols for rejection prophylaxis (*15*).

Rejection episodes were diagnosed by histologic examination, and graded as described previously (*5*). Treatment of rejection included initially high doses methylprednisolone (1 g/1.73 m^2 body surface area) for 3 days. Steroid-resistant rejection episodes were treated with antithymocyte globulins, 3 mg/kg/day for 10 days, or with OKT3 for 10 to 14 days, at a dosage of 2.5 mg/day in patients weighing less than 30 kg and 5 mg/day in others (*5, 15, 16*). Since mid-1990, patients with severe uncontrollable rejection, nonresponding to the above-mentioned regimen, were given FK506 as rescue therapy at a dosage of 0.15 mg/kg b.i.d. (*17*). In these patients, PRED was reduced to 0.25 mg/kg/day and other immunosuppressors were discontinued.

EBV Serology. Viral serology was performed regularly as described (*5*). This included determination of IgG antibodies to EBV early antigen (EA) and viral capsid antigen (VCA). Patients were considered as nonimmunized for EBV if antibody levels were VCA and EA ≤ 1/8 (*18*). For the present serological study, we selected 116 patients for whom EBV serology was available before transplantation and 6 months after transplantation. Ninety-one of these 116 also had serology performed at 1 year, and 57 of 116 at 2 years. These patients were divided into 2 groups, one without EBV immunity before transplantation (EBV VCA and EA titer ≤ 1/8; n=45), and one immunized for EBV before transplantation (EBV VCA or EA titer ≥ 1/16; n=71).

The mean EBV VCA an EA titers were calculated for each group at 0, 6, 12, and 24 months after transplantation, as follows: Serological values were converted into Log_2 values. The mean Log_2 value and standard deviation were calculated for the group, and the result was converted back to mean antibody titer by the formula: mean antibody titer = $2^{(\text{mean Log2 titer})}$ (Table 1).

The percentage of patients with positive EBV antibodies before transplantation is also given for the following age groups: 6–11 months old (n=15), 12–23 months old (n=31), 24–35 months old (n=26), 36–95 months old (n=26), and 96–168 months old (n=15).

Lymphoproliferative Disease. The diagnosis of EBV-associated lymphoproliferative disease was suspected in the following clinical situations: unexplained fever, lymphadenopathies, apathy, encephalopathy, gastrointestinal tract hemorrhage, respiratory distress, multiorgan failure, in presence or absence of clinically or radiologically detectable lymphoid tissue hyperplasia.

Only patients with demonstrated B lymphocyte proliferation were included. Patients with lymph node enlargement were not considered to have lymphoproliferative disorders if adenopathy was due to reactive T cell proliferation, and systematic T lymphocyte subtype determination was therefore made in such a situation.

Histological, immunological, and cytogenetic studies were performed to assess the specific characteristics of LPS according to the following protocol: (1) Histology and cytology: All involved tissues plus bone marrow specimen. Distinction between polymorphic or monomorphic infiltrate. B (Pan B, L26,MB2, CD19, CD21) and T (Pan T, CD3) cell typing by immunohistochemical determination of lymphocyte membrane markers on paraffin sections and/or frozen sections of organs involved, using different commercially available antibodies and immunohistochemical determination of κ and λ chains (*9–11, 19, 20*); and (2) cytogenetic study of the tumor and bone marrow specimen for determination of chromosomal abnormalities;

Mono- or polyclonality of the tumors where evaluated by the following analysis: (1) protein immunoelectrophoresis for the detection of oligoclonal or monoclonal bands of circulating immunoglobulin; (2) analysis of tumor cells for a monoclonal immunoglobulin gene reorganization; and (3) analysis of lymphocyte surface immunoglobulins.

RESULTS

All patients in the entire series of 261 children are regularly evaluated for general condition and liver function tests and none has been lost to follow-up.

EBV Serology. The mean EBV VCA and EA antibody evolution before and after transplantation in the groups of initially seropositive and seronegative patients are given in Table 1.

The percentages of patients with positive EBV antibodies before transplantation in each age group were: 6–11 months, 1/15=6.7%; 12–23 months, 16/31=51.6%; 24–35 months, 16/31=51.6%; 36–95 months, 20/26=77%; and 96–168 months, 10/15=67%.

Lymphoproliferative Diseases. Ten (7 girls) of 261 patients (3.8%) developed a well-characterized B cell lymphoproliferative disease. Six of them had developed a primary EBV infection after OLT, four in the few weeks before development of LPS and two 18–36 months before. The remaining 4 patients had past immunity for EBV at the time of transplantation, and 3 of them presented EBV antibody denivellation after OLT in the weeks before development of LPS (Table 2). The last one had no EBV antibody denivellation, being in bone marrow aplasia (OLT 299). Cross-match status, clonality, cariotype, and histology of the patients are reported in Table 3. Previous immunosuppression and organs involved in the B cell proliferation are detailed in Table 4.

Prolonged high fever and weight loss were prominent symptoms at presentation in all patients.

Outcome. One patient with initial adenotonsillar involvement died subsequently from bone marrow aplasia, after regression of her LPS. A second patient with mesenteric lymph node

* Abbreviations: EA, early antigen; LPS, lymphoproliferative syndrome; VCA, viral capsid antigen.

TABLE 1. Mean EBV antibody titer during follow-up in pediatric liver transplant recipients[a]

Pre-OLT status	Pre-OLT (n=116)		6 Months (n=116)		12 Months (n=97)		24 Months (n=50)	
	VCA	EA	VCA	EA	VCA	EA	VCA	EA
EBV negative (n=45, 39%)	0	0	1/49 ±5.8	1/14 ±2.5	1/96 ±7.3	1/25 ±3.6	1/191 ±10.3	1/55 ±4.3
EBV positive (n=71, 61%)	1/66 ±2.7	1/14 ±2.3	1/154 ±3.2	1/21 ±2.9	1/280 ±4.1	1/38 ±3.2	1/366 ±5.0	1/54 ±3.5

[a] Mean EBV antibody titer ± standard deviation (see *Patients and Methods*) during follow-up in 116 OLT recipients. EBV negative: group of initially seronegative patients; EBV positive: initially seropositive patients.

TABLE 2. EBV serology, timing, and outcome in 10 patients with LPS[a]

Patient	Pre-OLT		6 Months		12 Months		24 Months		36 Months		48 Months	
	VCA	EA	VCA	EA	VCA	EA	VCA	EA	VCA	EA	VCA	EA
107	neg	neg	neg	neg	64	8	1024	256	2048	256 neg	1024	128 neg
									Month 37 LPS		Alive & well month 72	
150	64	8	1024	128								
			Day 45: LPS died MOF									
153	neg	neg	neg	neg	1024	256	nd	nd	nd	nd	128	32
											Month 48 LPS died MOF	
171	32	8	32	8	nd	nd	128	64	128	64	128	64
							Month 30 LPS				Alive & well 52 months	
299	64	16	64	8								
			Day 90 LPS died BMA									
360	neg	neg	neg	neg	nd	nd	16	8				
							Month 24 LPS died MOF					
371	32	8	64	8	128	32						
					Month 9 LPS died MOF							
450	neg	neg	128	8	256	8	512	64				
			Month 3 LPS				Alive & well 24 months					
477	neg	neg	256	64	256	64	256	64				
			Month 7 LPS		Re-OLT		Alive & well 22 months					
530	neg	neg	128	8	64	8	128	8				
			Month 5 LPS		Re-OLT		Alive & well 20 months					

[a] EBV serology is given at 0, 6, 12, 24, and 48 months (or other timing indicated) after OLT in 10 patients with LPS. Timing of LPS is given for each patient, with the corresponding serology at that time. MOF, multiorgan failure; BMA, bone marrow aplasia. Retransplantation is indicated by "Re-OLT." Current follow-up is given for survivors.

involvement had regression after partial resection and prolonged arrest of immunosuppression, without any graft rejection episode during this 2-month period. Two additional patients with lymph node and digestive tract involvement had spontaneous regression of the syndrome after discontinuation of immunosuppression, but developed subsequent chronic rejection. They were successfully retransplanted without recurrence of the syndrome. All 3 patients with the disseminated form died rapidly in multiorgan failure. Among the 3 patients with the pseudotumoral form of the syndrome, complete resection of the tumor (the liver in one case) was performed in 2. Both are alive and free of disease. The third died from a huge retroperitoneal LPS involving the aorta, the inferior vena cava, and their branches. Two of these patients have received monoclonal antibody treatment (courtesy of Prof. A. Fischer, Necker-Enfants Malades, Paris, France) (*11*). One patient with a monoclonal liver tumor (OLT 477) received a 10-day course of anti-CD21 and anti-CD24 antibodies. She had partial tumor necrosis after treatment, but retransplantation was needed because of portal vein involvement with portal hypertension and biliary tract obstruction. The second patient (retroperitoneal mass) received anti-CD24 antibodies only, after evidence that 90% of the tumor cells were found to be CD24 positive. She did not respond to therapy and died shortly thereafter.

In summary, 5 patients are alive, 2 free of disease with the original graft and 3 free of disease but retransplanted. In all patients, immunosuppression was slowly reintroduced, either after retransplantation or after regression of LPS.

DISCUSSION

The 3.8% incidence of EBV-related lymphoproliferative disorders reported in this pediatric series is in agreement with incidences reported in other series of solid organ transplantation (*8–11*, *13*, *21*). It confirms previous findings that the incidence of posttransplant LPS is higher in children than in adults (*9*, *10*, *21*), since during the same period, only 2 (<1%) of 220 adult liver recipients developed this syndrome in our center (personal data). The incidence of LPS is also higher than that of solid tumors, since one single patient in our pediatric series developed this complication (*22*). The incidence of pretransplant EBV exposure in our patients was similar to that reported by Renard et al. (*21*). In the vast majority of initially seronegative patients, primary EBV infection occurred during the first 6 months to 1 year after transplantation, suggesting transmission of the virus by the graft and/or blood products. In both groups of initially seronegative and seropositive patients, the mean EBV antibody titers tended to increase with time after transplantation.

TABLE 3. Characteristics of 10 children with posttransplant B lymphoproliferative syndrome[a]

OLT	Cross-match	Clonality	Cariotype	Histology immunohistochemistry
107	neg	Ig: oligoclonal Mol biol: ND	Normal	Polymorph κ+, λ+, L26+, MB2+
150	+	Ig: oligoclonal Mol biol: ND	ND	Polymorph pan B+, κ+, λ+
153	−	Ig: oligoclonal Mol biol: clonal reorg Surf Ig: monoclonal IgMλ	No mitosis	Monomorph CD19+, CD21+, B+, κ+, λ+
171	+	Undetermined	Normal	Polymorph B+, κ, λ ND
299	−	Ig: polyclonal Mol biol: ND	ND	Polymorph B+, L26+, κ+, λ+
360	+	Ig: polyclonal Mol biol: polyclonal	Normal	Polymorph B+, L26+, MB2+, CD19+, CD3+
371	−	Ig: polyclonal Mol biol: ND	ND	Polymorph B+, κ & λ ND
450	+	Ig: polyclonal Mol biol: ND Surf Ig: polyclonal	Normal	Polymorph B+, κ+, λ+
477	+	Ig: monoclonal Mol biol: monoclonal	Normal	Polymorph B+, L26+, MB2+, CD21+, CD24+
530	−	Ig: oligoclonal Mol biol: oligoclonal	47XX+9 46XX−8+	Polymorph B+, κ+, λ+

[a] B, Pan B cell markers on paraffin sections of the tumors; κ, [kappa]-chains, λ, [lambda]-chains; L26 and MB2, B cell markers on paraffin sections; CD21, CD24, and CD19, B lymphocyte surface receptor on frozen tissue; CD3, T lymphocyte marker on frozen tissue; surf Ig, surface immunoglobulins on lymphocytes; ND, not done; +, positive test.

TABLE 4. Previous immunosuppression and organs involved in 10 children with lymphoproliferative syndrome

Patient	CsA/FK506	ATG[a] (mg)	OKT3 (mg)	Lo-Tact (mg)	Organ involved
107	FK506	150	50	—	Lymph nodes, digestive tract
150	CsA	250	81	—	Lymph nodes, liver, digestive tract, kidneys
153	CsA	—	25	—	Abdominal lymphoma
171	CsA	—	25	—	Mesenteric lymph nodes, ileal tumor
299	CsA	240	50	—	Tonsils, lymph nodes, liver
360	FK506	—	—	—	Tonsils, lymph nodes, brain
371	FK506	300	22.5	50	Tonsils, lymph nodes, liver, digestive tract, pancreas, adrenals, kidneys, lungs
450	CsA	—	—	—	Mesenteric lymph nodes, ovary
477	CsA	450	—	140	Liver tumor
530	FK506	250	—	—	Tonsils, lymph nodes, digestive tract

[a] ATG, antithymocyte globulin.

Four of the ten LPS patients developed their disease after EBV reactivation and 6 after primo infection. Although this shows that LPS does not necessarily follow primo infection, the higher rate of primo infection in pediatric patients may partly explain the higher incidence of LPS in pediatric patients than in adults (*21*, *23*).

These data demonstrate that EBV is one of the most frequent viral pathogens in pediatric liver transplant recipients. Although its exact pathogenic role in graft function remains to be established (*19*, *24*), it was clearly linked in our series with the development of the life-threatening complication LPS. The most widely accepted explanation is the loss of control by T suppressor cells of the proliferation of B lymphocyte clones infected by EBV (*9–11*). T cell cross-match status seems to interfere with this process either by continuous antigenic triggering or by the need for stronger immunosuppression (*11*, *23*). In our series, a 50% positive cross-match was observed, as compared with only 15% in the entire series (personal data), and all but one of our patients had had reinforced immunosuppression in the weeks before onset of LPS, most of them in the vicinity of EBV infection or reactivation. OKT3 has been incriminated in the development of LPS in cardiac transplant recipients (*9*), but such association did not reach statistical significance in a series of pediatric liver transplant recipients (*21*), and none of the OKT3-treated children at UCLA developed LPS (*16*). The development of this syndrome in our patients, except for one, was linked more with a cumulative effect of several immunosuppressors that these patients had received successively, ending up with the use of FK506 in 4 of them. Reports of patients treated with this compound as primary treatment have shown a similar incidence of LPS as in patients treated with CsA (*25*). Among the various presentations, patients with multiorgan involvement seem to have the worse evolution, since all died rapidly in multiorgan failure. An interesting finding was the regression of LPS despite cytogenetic abnormalities in patient 530, showing that these defects are not necessarily linked to poor prognosis. This patient had a polyclonal proliferation, and at least 2 different clones had different cytogenetic abnormalities.

In 3 of 5 survivors, cure of LPS was obtained at the cost of liver graft loss from chronic rejection or tumor resection.

We did not observe spontaneous regression of LPS after arrest of immunosuppression in the 2 patients with a monoclonal LPS, and they also failed to respond to monoclonal anti-CD21 and -CD24 antibody administration, in agreement with the reported poorer results of these antibodies in this situation (*11*). These observations confirm that monoclonality of LPS may be of poor prognostic value, unless complete resection is feasible, such as in patient 477 (*10, 23*). Although acyclovir was systematically given to the patients, as in most other series, the antiviral activity of this compound against EBV remains limited, and no clear benefit from this drug has so far been demonstrated (*26*).

In summary, EBV primo infection, reactivation, and related LPS represent a major long-term threat in liver transplant children now that life expectancy after OLT has increased (*5, 14*). However, by combining arrest of immunosuppression, acyclovir therapy, surgical excision, and retransplantation, 5 of 10 patients survived. Immunosuppression could be slowly reintroduced without recurrence of the syndrome.

We conclude that great care should be taken when immunosuppression needs to be strengthened in children with positive cross-match who have recently presented an EBV primo infection.

Immunosuppression must be stopped in any child developing B cell proliferation after OLT. Loss of the graft in our series was indeed an unavoidable step to save a patient's life. This latter complication is the most difficult decision for the physician.

Early recognition of the patients at risk (EBER 1 gene tissue detection) (*13*) added to the development of new therapeutic tools, such as monoclonal anti-CD21 and anti-CD24, and IL-6 antibodies, which may help cure these patients, without the need to stop immunosuppression and thus without losing the graft by rejection (*11*) (Prof. Fischer, personal communication, 1993).

Pretransplant vaccination of seronegative children when it becomes available should also play a major role in the prevention of this syndrome.

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Received 15 January 1993.
Accepted 19 May 1993.

0041-1337/93/5606-1399$03.00/0
TRANSPLANTATION

Vol. 56, 1399–1402, No. 6, December 1993
Printed in U.S.A.

PROLONGED PRESERVATION IN UNIVERSITY OF WISCONSIN SOLUTION ASSOCIATED WITH HEPATIC ARTERY THROMBOSIS AFTER ORTHOTOPIC LIVER TRANSPLANTATION

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Hepatic artery thrombosis (HAT) after liver transplantation (LTx) usually mandates retransplantation. Prolonged preservation with Eurocollins solution has been associated with HAT. We reviewed our experience with 359 LTx patients to identify risk factors for HAT. All grafts were preserved in University of Wisconsin solution. HAT developed in 12 patients (3%) within 50 days. Seven patients were asymptomatic; four presented with biliary sepsis and 1 with poor graft function. Two patients had suffered acute rejection; another 2 had severe preservation injury. Technical problems accounted for 4 cases; in the remaining 8, no etiology was found. Diagnosis was at a mean 14.7 days after LTx. One patient maintains normal graft function 3 years after LTx without intervention. Eight underwent re-LTx, 3 of whom died. Routine surveillance via duplex enabled early diagnosis and revascularization in 3 patients; in all 3, no biliary complications occurred between 6 and 20 months. Overall graft and patient survival after HAT were 33.3% and 75%, respectively. Cold ischemic time (CIT) averaged 813 min in patients with HAT and 669 min in those without HAT ($P<.05$). HAT occurred in 7/165 patients with CIT > 12 hr, and in 3/234 patients with CIT < 12 hr ($P=0.0699$). By avoiding CIT > 12 hr, we have recently avoided HAT in 78 consecutive patients. We conclude that CIT > 12 hr may increase the risk of HAT. When HAT is diagnosed before biliary sepsis develops, flow can often be restored and retransplantation averted.

Whereas hepatic artery thrombosis (HAT)* after OLT once mandated retransplantation (*1*), postoperative screening with Doppler ultrasonography now makes it possible to diagnose HAT in asymptomatic patients, permitting prompt thrombectomy with or without vascular reconstruction (*2–4*). Nevertheless, HAT remains a major complication of OLT. Technical problems (*2–4*), hypercoagulable states (*5*), low flow or severe hypotension (*3*), rejection (*6*), and prolonged cold ischemia time in Eurocollins solution (*7*) have all been implicated in the pathogenesis of HAT. We reviewed our experience with patients who developed HAT within 50 days of OLT and found that extended cold preservation in University of Wisconsin solution is associated with increased risk for HAT. Considerations of the surgical approach to this problem are discussed in detail, with reference to our own experience and to reports in the literature.

PATIENTS AND METHODS

Between July 1988 and July 1992, 419 liver transplants were performed in 359 patients, including 322 adults and 37 children. The recipient common hepatic artery was the preferred site for anastomosis, although the proper hepatic or the splenic artery (*8*) were used occasionally. In 30 patients, donor iliac artery graft was used as a conduit from the recipient aorta for the following reasons: small diameter of the recipient hepatic artery, intimal dissection, and recipient celiac artery stenosis.

Hepatic arterial and portal vein flow measurements were made between 1 and 2 hr after reperfusion using an electromagnetic flowmeter (Cliniflow II, model FM 701D; Carolina Medical Electronics, King, NC). Hepatic artery flow was measured first in the resting state, and then 30 sec after occlusion of the portal vein (augmented hepatic artery flow). Percentage of augmentation, defined as the difference between the augmented hepatic artery flow and the resting flow, divided by the resting flow, was calculated. Doppler ultrasonography (Duplex) was performed routinely on the second postoperative day in adults, and every day for the first week in children who weighed less than 15 kg. When flow could not be demonstrated in the hepatic artery, celiac angiography was performed, although occasionally duplex ultrasonography was repeated after administration of nifedipine (10 mg sublingual). All patients received aspirin (60 mg p.r. or 81 mg p.o.) for prophylaxis of thrombosis; in addition, children (weight < 15 kg) were given intravenous heparin (5–10 U/kg/hr) for the first week.

Immunosuppression was induced and maintained with CsA, steroids, and AZA according to our previously described protocol (*9*); occasionally, patients with renal failure received OKT3 induction. Twenty-seven patients were managed primarily with FK506 and steroids.

Revascularization after HAT was accomplished by thrombectomy and, if necessary, excision of the thrombosed segment up to the bifurcation of the proper hepatic artery. In 2 patients, donor iliac artery grafts were used to bridge the gap between recipient and donor artery.

The groups with and without HAT were compared. For all patients, operative data (i.e., variations in hepatic artery anatomy and the need for back table reconstruction, cold and warm ischemia times, and arterial flow measurements) were examined. For patients with HAT, clinical signs and aminotransferase (aspartate aminotransferase and alanine aminotransferase) levels at the time of diagnosis were noted, as were the extent of preservation injury and the occurrence of rejection.

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* Abbreviation: CIT, cold ischemia time; HAT, hepatic artery thrombosis.