TABLE 3. The impact of blood pressure instability and pulmonary dysfunction on hepatocellular damage in 190 liver allografts

Variable	Category	No. patients	AST or ALT >2000 U/ml		P
			No. patients	%	
Dopamine	≤15	149	24	16.1	
(μg/kg/min)	>15	41	11	26.8	0.170
BP <90 mmHg	No	130	19	14.6	
	Yes	60	16	26.7	0.069
BP + dopamine	No	112	11	9.8	
	Yes	23	10	43.5	0.00033
pO_2 <70 mmHg	No	154	27	17.5	
	Yes	36	8	22.2	0.484

TABLE 4. Causes of graft loss and patient death within the first 2 weeks of transplant in 365 liver transplants

Cause	No. grafts	%	Retransplantation	Death
PNF[a]	10	34.5	10	2
Rejection	7	24.1	4	3
Sepsis	5	17.2	0	5
HAT[b]	1	3.4	1	0
Cardiac	3	10.3	0	3
CNS	2	6.8	0	2
Other[c]	1	3.4	0	1
Total[d]	29	7.9	15	16

[a] Primary nonfunction.
[b] Hepatic artery thrombosis.
[c] Splenic artery aneurism rupture.
[d] Graft loss and mortality rates based on 365 grafts in 313 patients.

infiltration, it is reasonable to selectively examine the liver during the retrieval by a frozen-section biopsy, in such donors. Prolonged stay in the ICU and the presence of a profound shock were both associated with increased hepatocellular damage. Finally, although about 70% of early hepatocellular injuries were reversible (*18*), we have demonstrated an increased rate of rejection associated with this type of injury (*19*), and the remaining 30% developed primary graft failure. We are still lacking precise parameters to predict postoperative liver graft function. The future use of dynamic studies, such as the indocyanine green test, galactose excretion test, or lidocaine metabolism assay (MEGX), may allow quantitative measurement of liver functional capacity in order to better predict the outcome (*20*). Combining all these data, it is still the transplant surgeon's own judgment and expertise that are the mainstay of sound organ procurement.

Acknowledgments. We are grateful to Linda Jennings, Ph.D., and Kathy Koch for help with the data collection and statistical analysis and to Southwest Organ Bank for providing the donor data.

ORAL DISCUSSION

DR. ROHR (Winston-Salem, NC): Were any of these donors maintained using hormonal support?

DR. MOR: We haven't studied hormonal changes in the donor, but we plan to do so.

DR. ASCHER (San Francisco, CA): We are all interested in expanding the pool for liver donors. We heard this morning that extended preservation time was associated with nonischemic bile duct obstruction. Do you have any comments or data regarding this?

DR. MOR: Well, I too just heard this today; we will have to determine whether our data showed any correlation.

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THE RESULTS OF REDUCED-SIZE LIVER TRANSPLANTATION, INCLUDING SPLIT LIVERS, IN PATIENTS WITH END-STAGE LIVER DISEASE[1]

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We initiated a policy of using RSLT in critically ill patients in June of 1988. Since that time we have performed 30 RSLTs in 29 patients, including 28 children and 1 adult. The mean age of the children was 27 months (range 1 month to 10 years) with 14 (52%) being 1 year of age or less. The mean weight was 11.3 kg (range 2–50 kg) with 20 being 10 kg or less. A total of 22 patients were in the intensive care unit at the time of RSLT including 9 who were intubated. Of the 30 RSLTs, 23 were performed as a primary transplant while 7 were retransplants. Indications for primary transplantation included biliary atresia (n=11), fulminant hepatic failure (n=5), neonatal hepatitis (n=4) and others (n=3). The RSLT was used in retransplantation for primary nonfunction (n=2), hepatic artery thrombosis (n=2), chronic rejection (n=2), and herpetic hepatitis (n=1). The size reductions included 18 left lobes, 7 left lateral segments, and 5 right lobes. This group includes the use of the split-liver technique, which was applied to 10 patients (5 livers). The median donor/recipient weight ratio for left lobe transplants was 2:1; left lateral segments was 7.3:1; and right lobes 1.6:1. One year actuarial patient and graft survivals were 68 and 65%, respectively, with a mean follow-up of 10.6 months. The number of children dying awaiting transplantation has been significantly reduced following the introduction of RSLD (3 of 115, 2.6% vs. 12 of 95, 13%; $P<0.02$).

The major limitation to wider use of solid-organ transplantation continues to be a shortage of donor organs. This has been particularly problematic for children awaiting liver transplantation. Malatack and coworkers at the University of Pittsburgh reported that 25% of children died prior to the procurement of a suitable liver (*1*). In 1984, compelled by the lack of size-compatible donors, Bismuth and coworkers described the first reduced-size liver transplant (RSLT) (*2*). Following this pioneering effort, several groups reported their initial attempts with RSLT (*3–5*). In 1988, the introduction of University of Wisconsin preservation solution into clinical trials removed the logistical constraints often associated with RSLT. Despite growing enthusiasm for RSLT, concerns have been raised regarding the number of graft-related complications and the possibility that RSLT may be diminishing the donor pool for one group of recipients to satisfy the needs of another.

Dismayed by the death of children awaiting transplantation at our institution we initiated a program of RSLT in June of 1988. In this report, we describe our experience with RSLT, including recipient characteristics, surgical techniques, overall results, and the impact of RSLT on waiting list deaths.

MATERIALS AND METHODS

Surgical technique. Size reduction was performed after the donor organ arrived at the recipient center and before beginning the recipient operation. The initial back-table preparation of the liver was similar to that used for whole-organ transplants. After making a decision regarding the volume of reduction required, we performed a transparenchymal division of the liver based on the previously described technique of Otte and coworkers (*3*). This was accomplished with a large amputation knife, providing a smooth surface to facilitate suture ligation of the numerous vascular structures and biliary radicals. This technique was altered when split liver transplants were used. In this setting we performed an extensive hilar dissection to delineate the vascular supply to both halves of the liver prior to the ex vivo hepatic division (*6*). This allowed for the proper allocation of blood vessels (Fig. 1).

The liver was implanted orthotopically. We did not routinely rotate left hepatic lobe grafts about their caval axis. Left lateral segment grafts were revascularized without the use of vascular grafts, and venous outflow was provided by the left hepatic vein which drained directly into a single stoma made of the remnants of the recipient hepatic veins. Hemostasis along the raw liver surface was obtained with electrocautery, suture ligation of vessels, and the application of fibrin glue. Biliary reconstruction was performed by Roux-en-Y choledochojejunostomy. All patients received aspirin postoperatively.

We retrospectively reviewed the charts of all patients undergoing RSLT from June 1988 through January 1991. During the period of study, uniform protocols for donor management, organ retrieval, and immunosuppression were followed. We examined several patient variables including age, weight, ICU status, and indications for transplantation. Graft related complications were also recorded, including vascular thrombosis, primary nonfunction, and biliary tract complications. Also, noted were actuarial patient and graft survival rates. These results were then compared with those obtained in the remaining children, 10 years old or less, who underwent whole-liver transplantation. We retrospectively evaluated the number of children who died awaiting liver transplantation.

Statistical analysis. Univariate analysis was performed with the unpaired Student's *t* test for continuous variables, the chi-square test for categorical variables, and the Fischer's exact test when data were sparse. Actuarial survival were computed by the Wilcoxon life-table analysis. A probability value of <0.05 was considered significant.

RESULTS

Twenty-nine patients underwent a total of 30 reduced size liver transplants (28 children and 1 adult). The mean age of the children was 2.2 years (1 month to 10 years). Twenty-one (71%) of the children weighed less than 10 kg, and 14 (50%) were less than 1 year of age. Twenty-two (73%) were in the intensive care unit at the time of transplantation, including

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nine who were intubated. All patients were hospitalized at the time of transplantation. Of the 30 RSLTs, 23 were performed as a primary transplant while 7 were retransplants. Indications for primary transplantation included biliary atresia (n=11), fulminant hepatic failure (n=5), neonatal hepatitis (n=4), and others (n=3). The RSLT was used in retransplantation for primary nonfunction (n=2), hepatic artery thrombosis (n=2), chronic rejection (n=2), and herpetic hepatitis (n=1).

Of the 30 RSLTs there were 18 left lobe, 7 left lateral segment, and 5 right lobe allografts. This included 5 split livers (5 left lateral segment and 5 right lobe allografts). The median donor:recipient weight ratio for left lobe RSLT was 2:1 (range 4:1 to 1.2:1), left lateral segments 7.3:1 (range 11.2:1 to 2.5:1), and right lobe RSLTs 1.6:1 (range 2:1 to 1.2:1). The mean operative time for these patients was 7.39±2.63 hr, with a mean blood transfusion requirement of 1.37±1.20 blood volumes. A comparison of these variables with recipients of whole-liver transplants revealed a significantly greater blood requirement for recipients of RSLT (Table 1).

A number of graft-related complications occurred and are listed in Table 2. There were no cases of hepatic vein occlusion. We compared these results with children undergoing full-size liver transplantation and no significant differences were noted (Table 2).

The one-year actuarial patient and graft survival rates for RSLTs were 69% and 67%, respectively, with a mean follow-up of 10.6 months (Fig. 2). We compared the survival rates of patients undergoing RSLTs with children 10 years old and less who received whole-liver allografts. These recipients of whole livers were segregated into urgent and elective groups. The elective group consisted of children who came from home for transplantation while the urgent group were hospitalized. While there was no difference in patient survival when comparing the RSLT with the urgent whole-liver group, there was a diminished survival when compared with the patients undergoing elective transplants (Fig. 3). We also compared length of hospitalization and ICU stay between children receiving RSLTs and those undergoing whole liver transplants segregated into elective and urgent groups. Only ICU stay in the elective whole-liver transplant group was significantly different. The current liver function tests of the surviving recipients of RSLT include a mean bilirubin of 0.6 mg/dl ±0.3 (median 0.5, range 0.2–1.8), a mean serum glutamic-pyruvic transaminase of 41 U/L ±57 (median 24, range 10–154), and a gamma-glutamyl transpeptidase of 112 IU/L ±246 (median 33, range 4–1041).

There were nine deaths. Three patients died as a result of primary nonfunction; one of these died despite retransplantation with a functioning RSLT. The remaining two patients received grafts from the same split liver, one as a primary transplant and the other as a second graft as a result of fulminant herpetic hepatitis. The remaining deaths were not related to graft failure. The specific cause of death in each of the nine patients is listed in Table 3.

Prior to the use of RSLT, 12 of 98 (13%) of the children on our waiting list died prior to transplantation. However, since the introduction of RSLT only 3 of 113 (2.6%) children have died prior to transplantation. One of these children died awaiting a primary transplant while the other two were awaiting their second transplant. These results represent a significant improvement in the number of waiting list deaths (12 of 98, 13% versus 3 of 113, 2.6%; $P<0.05$).

DISCUSSION

The results of this study reinforce the findings of others that RSLT represents a safe and effective tool for the treatment of end-stage liver disease in children. This was represented by one-year actuarial patient and graft survival rates of 69% and 67%, respectively, in a group of critically ill patients. These results are similar to those reported by Otte and coworkers, who reported 68% and 54% patient and graft survival rates (*3*). While we did note a diminished survival when compared with children receiving elective transplants, we believe that this represents primarily the influence of pretransplant comorbid factors.

One of our major concerns when initiating a program of RSLT would be that the increased complexity of these procedures would increase the rate of graft-related complications

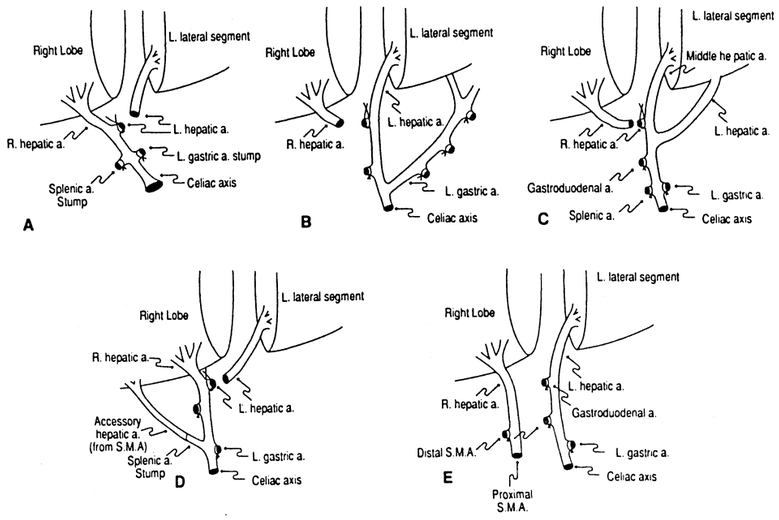

FIGURE 1. (A–E) Methods of arterial reconstruction used for split liver transplantation.

TABLE 1. Intraoperative variables: RSLT versus whole liver

	RSLT transplants (n = 30)	Whole transplants (n = 155)	P
Operative time (hr)	7.39±2.63	7.40±2.23	NS
Blood requirements (blood volume)	1.37±1.20	0.74±0.98	$P<0.001$

TABLE 2. Graft-related complications: RSLT versus whole liver

	RSLT transplants (n = 30)	Whole transplants (n = 155)	P
Biliary tract	6 (20%)	18 (12%)	NS
Abscess	5 (17%)	12 (8%)	NS
Primary nonfunction	3 (10%)	7 (5%)	NS
Hepatic artery thrombosis	2 (7%)	16 (10%)	NS
Portal vein thrombosis	0	4 (3%)	NS
Total	16 (53%)	57 (37%)	NS

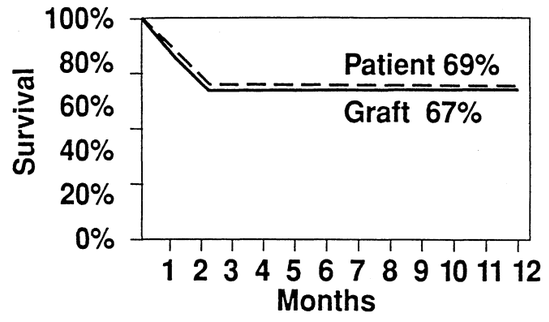

FIGURE 2. One-year actuarial patient and graft survival for recipients of RSLT.

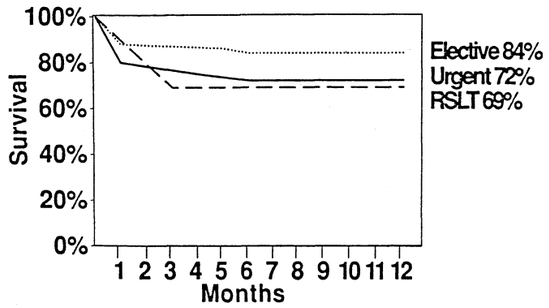

FIGURE 3. Comparative patient survival. (Urgent) recipients of a whole liver, <10 years old, hospitalized at the time of transplant. (Elective) recipients of a whole liver, <10 years old, coming from home for transplantation. (RSLT) recipients of RSLT—all hospitalized at the time of transplantation.

and possibly graft loss. The results of this report revealed a 53% incidence of graft-related complications. While this was somewhat greater than patients undergoing whole-liver transplants, there was not a significant difference. Broelsch and coworkers reporting on 61 RSLTs noted a 75% incidence of graft-related complications (*7*). They suggested that while this might be considered unacceptable for recipients of whole-liver

TABLE 3. Comparison of length of hospitalization and ICU stay for recipients of RSLT, and children <10 years old, receiving whole livers—based on preoperative status

	RSLT (n = 29)	Whole (n = 130)	
		Urgent (n = 49)	Elective (n = 81)
Hospitalization (days)	58±40	68±48	47±34
ICU stay (days)	33±32	26±32	14±17[a]

[a] $P = 0.007$.

TABLE 4. Major causes of death (n = 9)

	n
Primary nonfunction	3
Cerebral injury/sepsis	2
Peritonitis	1
Prematurity/peritonitis	1
Rejection	1
Midgut volvulus	1

grafts, the patients receiving RSLTs represented a unique group of high-risk recipients. We do not, however, think that the graft-related complications in our series were related to recipient characteristics, but rather to the learning curve associated with a new surgical procedure. Otte and coworkers reporting on their experience with RSLT noted similar rates of graft loss for both full-size and reduced-size transplants as a result of hepatic causes (*3*). This was similar to our experience.

It has been suggested by Broelsch and coworkers, (*7*) as well as Otte and associates (*3*), that the incidence of hepatic artery thrombosis may be reduced in patients with RSLTs. Proposed reasons include the larger size of vessels for anastomosis and decreased vascular resistance within the graft. We could not confirm this finding. The incidence of hepatic artery thrombosis was similar for reduced-size and whole-liver transplants.

Broelsch and coworkers also expressed concern over the relatively frequent occurrence of hepatic vein occlusions in recipients of left lateral segment grafts (*7*). We have used a similar technique of anastomosing the left hepatic vein to the recipient vena cava in an end-to-side fashion. We observed no cases of venous outflow obstruction and think that this has been accomplished by using as short a left hepatic vein segment as possible.

The degree of size reduction is determined by a number of factors, including the donor and recipient weights. The final decision, however, is based on the relative size of the right and left lobes of the donor liver, combined with knowledge of the size of the recipient liver. When these parameters do not provide satisfactory information, we will remove the donor liver segment from the back table and hold it directly over the recipient while the anesthesiologist prepares the patient. We routinely remove the caudate lobe, which not only reduces the sagittal diameter of the liver but facilitates caval mobilization. This has allowed us to tailor the volume of left lobe grafts by removing portions of the medial segment. Unfortunately, further size reduction of left lateral segment grafts cannot be performed. In two cases left lateral segment grafts proved to be too large and abdominal wall mesh was required for closure. In both cases, based on previous experience the volume reduction would have been appropriate. However, both recipients had shrunken livers with very small hepatic fossae.

The technique of split liver transplantation was first reported by Pichlmayr in 1988 (*8*). The enticing nature of this procedure was that it could provide two functioning allografts from one donor liver. We have limited our use of this procedure to critically ill patients. The use of SLT adds considerable complexity to the transplant procedure. The most difficult aspect of the SLT technique is the appropriate separation of arterial and biliary systems. In each of the five livers divided, a different arterial pattern was noted (Fig. 1). Although we use a transparenchymal technique for creating reduced-size liver grafts, we think a hilar approach is preferred for split-liver transplants. While this allows us to safely identify the vascular anatomy, the risk of devascularizing the bile duct is increased.

The role of split-liver transplantation for adults recipients remains controversial. Emond and coworkers reported on 5 adults receiving right lobe grafts following split-liver transplants, of whom 4 died (*9*). Based on our experience with 1 patient and on that of others, we have not performed any further reduced-size liver transplants in adult recipients.

Prior to the introduction of reduced-size liver transplantation, Matlack and coworkers at the University of Pittsburgh reported that 25% of children died awaiting liver transplantation (*1*). A major factor contributing to this problem was the disparity in age of children requiring liver transplantation and the age of potential pediatric organ donors. We were also plagued by this problem, with 13% of our pediatric liver transplant candidates dying while awaiting a suitable donor organ. However, since we began using reduced-size liver transplants in June of 1988 only 3 children have died prior to transplantation. This may be a result of a number of factors, including organ availability and the relative number of patients on the waiting list.

In conclusion we think that RSLT represents a safe and effective therapy for critically ill children suffering from end-stage liver disease. While there were a number of graft-related complications, the incidence was not significantly greater than that seen for recipients of whole-liver grafts. We believe the one year actuarial patient and graft survival rates of 69 and 67%, respectively, reflect the pretransplant condition of these recipients, as demonstrated by their small size, young age, and large number in the intensive care unit at the time of transplantation. The major impetus for developing a policy of RSLT was to reduce the number of children who died awaiting transplantation, which we believe has been successful.

ORAL DISCUSSION

DR. BROELSCH (Chicago, Illinois): It is exciting for me to see the progress in thinking over the past five years since we reported the first U.S. experience with segmental liver transplantation. You may recall the initial controversy as to whether reduced-size transplants should be performed at all. Some proposed that the approach would shift the major donor shortage from the pediatric side to the adult side. You have combined the split transplants with the reduced-size transplants without differentiating complications to one of the approaches. Can we assume the splits were as good as the simple reduced-size liver transplants?

Although we all can understand the potential for the split transplant in alleviating the donor shortage, we previously reported inferior results with the split approach. What is your present policy for performing the splits? Why have you only done 10? Do you foresee technical problems, or is the problem primarily logistic?—that is, because each procedure requires two operating rooms, two ICU beds, two operating teams, etc.

DR. LANGNAS: We currently limit this technique only to critically ill recipients. The situation of having 2 patients of the proper weight, size, and severity of illness occurring simultaneously does not occur frequently. We do not, at this time, advocate the use of a split liver transplant for the elective patient. Based largely on your experience at the University of Chicago, and our experience with the one patient in this report, we have generally not applied this technique to the adult recipient population.

DR. B.W. SHAW (Omaha, Nebraska): Although in many ways it seems logical to transplant the right lobe into an adult recipient, and the left lateral segment into a child, I've had a problem with informed consent. Can we explain the rationale for giving an adult recipient only part of a liver? Our total experience is relatively limited, we really do not know the risks.

Dr. Broelsch, can you provide us an idea as to the overall risk for an elective adult patient receiving a right lobe transplant? Might it be greater than if they were transplanted with the whole liver?

DR. BROELSCH: Your question gets right to the point, that is how to obtain informed consent from the recipient of a right hepatic lobe. Our experience, yours, and that of the group in Hannover, Germany suggests that the results for the split transplants are 10–15% inferior to the regular type of full-sized transplant.

However, I believe the procedure should be studied in a prospective fashion. We now have more experience with the reduced-size transplants. Today, we could approach patients with the proposal that the risk is likely similar to full-size transplants. Again, we can't prove this now, but the procedure should proceed as part of a prospective study. It could lead to a scenario, for example, where a full-sized liver is harvested in one part of the country with portions being sent for transplantation to 2 other areas. Until we embark upon such a study, our data will remain limited. I believe the time has come to address this issue, or we may all have to consider transplanting living-related segments. We have to do more transplants on adults, including alcoholics and perhaps tumor patients; we have to provide more donor organs.

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BILIARY COMPLICATIONS IN PEDIATRIC LIVER TRANSPLANTATION

A COMPARISON OF REDUCED-SIZE AND WHOLE GRAFTS[1]

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One of the major changes in liver transplantation has been the application of reduced-size liver transplants(RLT). RLT has the great advantage of expanding the donor pool up to ten times the weight of the recipient, thereby decreasing pretransplant mortality in the pediatric age group. It has been suggested that RLT is a risk factor for biliary complications. To analyze the role of RLT and biliary complications, the results of 213 consecutive liver transplants in 164 pediatric patients over a 6-year period will were reviewed. These included 113 whole-liver transplants and 100 reduced-size liver transplants (49 reduced cadaveric liver transplants (RCLT), 38 split-liver transplants (SLT) and 13 living-related liver transplants (LRLT). The average weight and age were significantly higher in recipients receiving whole-size grafts (average weight 18.4 mg, average age 4.9 years) than in those receiving reduced size grafts (average age 2.3 years, average weight 11.1 kg).

Biliary reconstruction consisted of Roux-en-Y, cholangiojejunostomy (n=203) or choledochocholedochostomy (n=10). There were 29 total biliary complications, (13.6%) with no significant difference in the complication rate between the whole (n=13, 11.5%) or reduced livers (n=16, 16%). Biliary leakage was the most common complication (n=20), and it occurred at the biliary enteric anastamoses (n=10), the roux limb (n=7), or at the cut edge (n=3). Of the leaks occurring at the biliary enteric anastomoses, 50% were caused by hepatic artery thrombosis. Biliary obstruction accounted for their remaining complications (n=9) or 4.2%. Actuarial survival from 6 years to a minimum of two months of follow-up was 73% in the whole-size and 70% in reduced-size liver transplants. This series demonstrates that the incidence of biliary complications is similar in reduced-size and full-size grafts. No grafts were lost to biliary complications in the absence of hepatic artery thrombosis.

One of the major advances in pediatric liver transplantation has been the application of reduced-size liver transplantation (RLT).* In 1987, prior to reduced size liver transplantation becoming standard practice at many centers, Matalack analyzed the fate of children referred to the University of Pittsburgh for OLT and documented that 25% of the children accepted as candidates died before a liver became available (*1*). First reported by Bismuth and Broelsch in 1984 (*2, 3*), RLT has the great advantage of expanding the donor pool up to 10 times the weight of the recipient, thereby decreasing pretransplant mortality in the pediatric age group. In the last several years, reduced-size liver transplantation for pediatric patients has become a standard procedure at many centers specializing in pediatric liver disease (*4–8*). Reduced-size liver transplants consist of reduced cadaveric transplants (RCLT), split-liver transplants (SLT) and living-related liver transplants (LRLT) (*9*).

In the early experience with liver transplantation, biliary problems were a leading cause of morbidity and mortality (*10*). In 1977, Calne characterized biliary construction as a technical Achilles heel of liver transplantation (*11*). Despite a significant improvement coinciding with technical and immunological advances, biliary complications remain a significant cause of morbidity. Even in the nontransplant population, a morbidity rate of approximately 15% has been associated with biliary

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* Abbreviations: LRLT, living-related liver transplant; RCLT, reduced-size cadaveric liver transplant; RLT, reduced-size liver transplant; SLT, split-liver transplant.