Extrahepatic Biliary Atresia

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Liver Transplantation for Biliary Atresia

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INTRODUCTION

To put the subjects of biliary atresia and liver transplantation into perspective, I will first discuss our total case material, summarize our results in all pediatric recipients, and finally focus upon the subset of patients with biliary atresia.

The first long-term survival after liver replacement was a dog whose new liver came from a nonrelated mongrel donor in 1963. The animal lived a full canine lifetime, finally dying of old age almost 12 years later. That longevity record has now been superseded by a girl with biliary atresia who was given a new liver 12 years ago and is now in high school. When her diseased liver was sectioned after its removal, we were stunned to find a 2-cm hepatoma. Serum α-fetoprotein was about 6 mg %. No tumor recurrences have been seen in the intervening years.

CLINICAL TECHNICAL CONSIDERATIONS

The procedure of orthotopic liver transplantation consists of removal of the diseased native liver and its replacement with the liver of a cadaveric donor. This is now an easier undertaking partly because of the widespread acceptance of brain death in the United States. One can preserve livers relatively safely for about 8 h with good expectation of a successful transplantation. This development in preservation relieved the logistic burdens from which we were previously suffering, whereby it was necessary or highly desirable to have the donor and recipient in the same hospital and, hopefully, in adjacent operating rooms. Now it is quite possible to collect a liver in a community hospital and transplant it in a distant major medical center (1).

The recipient operation for the placement of a new liver is very straightforward. It consists of an anastomosis of the inferior vena cava above and below the liver and the reconstruction of the portal triad structures. The ideal form of biliary tract reconstruction is with a duct-to-duct anastomosis, but in patients with biliary atresia that obviously is not feasible. In the early days, we often ligated the distal common duct of the homograft and anastomosed the gallbladder to the duodenum. This was a procedure of convenience, but it proved disastrous. In recent years, despite the smallness of the common duct of the pediatric livers, we have anastomosed the common duct directly into a Roux limb of jejunum. This solution to biliary drainage is more satisfactory, in most cases, than the alternative of connecting the gallbladder into the defunctionalized Roux limb (1).

When we first began treating patients who had previously undergone Kasai operations, the Roux limbs were uninterrupted by ostomy side vents, which have since become common. The Roux limbs could usually be reused at the time of transplantation. With the more complicated Kasai procedures in which skin jejunostomies have been constructed (and often closed later), it has almost always been necessary to take down the Roux limb, often with difficulty, and to begin over. Thus, as worthwhile as it is, the Kasai operation does pose certain technical difficulties for eventual transplantation.

ADULT AND PEDIATRIC CASES (1963-1979)

The end of 1979 concluded an era in which patients were treated with the conventional immunosuppression, consisting of azathioprine, prednisone, and often antilymphocytic globulin (ALG). There were 169 recipients, of whom 86 were 18 years or younger. An almost equal number (83 patients) were adults, whose indications for operation are summarized in Table 1. Chronic active hepatitis was the most common hepatic disorder in the adults.

Table 1 Indications for Transplantation: 1963-1979 (Adults 19-70 Years)

Chronic active hepatitis	32
Primary liver malignancy	16
Alcoholic cirrhosis	16
Primary biliary cirrhosis	7
Sclerosing cholangitis	6
Secondary biliary cirrhosis	3
Massive hepatic necrosis (B virus)	1
Budd-Chiari syndrome	1
Protoporphyria	1
Total	83

During the same 16-and-2/3-year period, 86 patients in the pediatric category were treated with orthotopic liver transplantation (Table 2). There were 53 cases of biliary atresia, four times as common an indication as the next most common category, inborn errors of metabolism. Twelve pediatric recipients had chronic active hepatitis (Table 2). Immunosuppressive therapy was similar in adults and children and was adapted from treatment protocols which were standardized with simpler renal transplantation models. With azathioprine, prednisone, and ALG, while it was possible to succeed in some cases of liver transplantation, there was very little margin of safety and loss rates were unacceptable. The actual life survival curves from 1963 to the end of 1979 are summarized in Figure 1. In our original series (the first long-term survival was achieved in 1967), about two-thirds of the patients died by the end of the first postoperative year. In a second, smaller series in which many improvements in techniques and management were instituted, the 1-year survival rose to 50%, but this proved to be a fluke. In the third series which followed, the data once again were similar to those of the original group. This was an unsatisfactory situation, which caused many people to wonder if such extreme efforts as those that were required in these trials could be further justified.

During those lean years, 16 (30.2%) of the 53 patients with biliary atresia lived for as long as 1 year (Table 3). The one justifying aspect of the undertaking was that eight of those survivors are still living after 4-12 years. During the same time, when the 53 patients with biliary atresia were observed, 33 pediatric recipients with other hepatic disorders were treated at the University of Colorado. The 1-year survival of the biliary atresia patients of 30.2% was distinctly inferior to that achieved in children who had other diagnoses, of whom more than half were alive at the end of the first postoperative year (Table 3). Subsequent to a year, the advantage of having diagnoses other than biliary atresia has persisted (Table 3). Today only about one in seven (15%) of the biliary atresia recipients are still living (Table 3).

Table 2 Indications for Transplantation: 1963-1979 ($\leq$ 18 Years)

Biliary atresia	53
Inborn metabolic errors	13[a]
Chronic active hepatitis	12
Hepatoma	3
Neonatal hepatitis	2
Congenital biliary cirrhosis	1
Congenital hepatic fibrosis	1
Secondary biliary cirrhosis	1
Total	86

[a]Inborn errors: α_1-antitrypsin,9; Wilson's Disease, 2; tyrosinemia, 1; type IV GSD, 1.

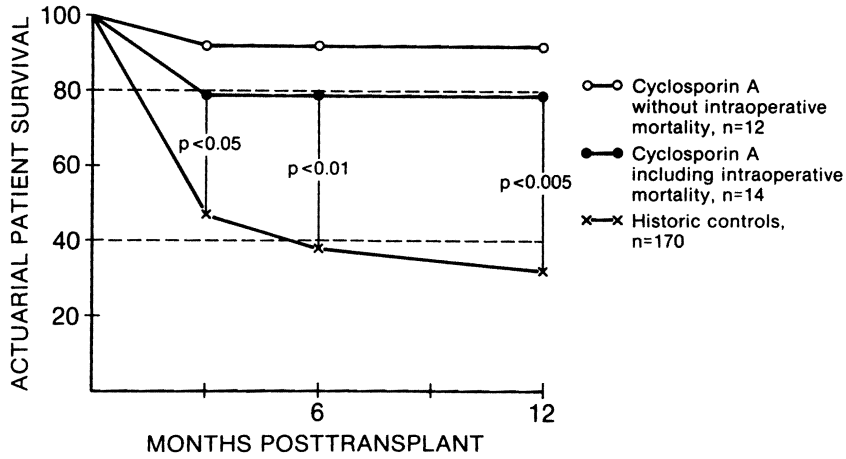

Figure 1 One-year actuarial survival in patients given liver transplants. The follow-up period ranged from 8 to 14½ months. The open circles represent survival in the 12 patients who lived through the operation and who were treated with Cyclosporin A and prednisone; the solid circles represent survival in all 14 patients who underwent transplantation (including the 2 who died during the operation); and the crosses represent survival in 170 patients from a previous series who were treated with conventional immunosuppression. (Modified from Ref. 9 by permission of the *New England Journal of Medicine 305*:266, 1981.)

EMERGENCE OF CYCLOSPORIN A

After laboring in these barren vineyards for many years, it was our conclusion that there was virtually no margin of safety with liver transplantation under conventional immunosuppression. We were constantly on the lookout for improvements in immunosuppression, and such an improvement came to light in 1976 in a journal called *Agents and Actions*. Borel and his associates of the Sandoz Corporation, Basel, Switzerland, had done a magnificent job of character-

Table 3 Pediatric Transplantation: 1963–1979

	Number	1-year survival	Alive now
Biliary atresia	53	16 (30.2%)	8 (15.1%)[a]
Other diseases	33	17 (51.6%)	12 (36.4%)[b]

[a]4–12 years.
[b]2–11 years.

izing cyclosporin A and its immunosuppressive qualities, including specific testing of skin grafts in rats (2). Furthermore, Sandoz chemists fully characterized the structure of this agent almost at the outset. The agent was released for limited animal work in 1977 and 1978, for clinical trial in Britain in 1978 (3), and at two centers in the United States in 1979. The first American clinical trials were at the University of Colorado and at the Peter Bent Brigham Hospital in Boston. Results with cyclosporin A were profoundly encouraging in some centers, but not in others. At Cambridge, England (4), and in Colorado (5,6), the survival of primary cadaveric kidney recipients was exceptionally high, 80% or better, but at the Peter Bent Brigham Hospital (7) and at the Royal Free Hospital in London (8) the results were disappointing. We think that the reason for our success with cyclosporin was its combination with low doses of steroid (5,6).

CYCLOSPORIN A-STEROID THERAPY AND LIVER TRANSPLANTATION

After 25 kidney recipients had been treated with the combination of cyclosporin A plus steroids, a decision was made to use this therapy for adult liver recipients. The dose of cyclosporin A (17.5 mg/kg per day) was combined with variable dosages of prednisone, usually in the range of 20 mg/day. For the first time, it became possible to effectively control liver rejection without a tremendous penalty in terms of chronic high-dose steroid therapy.

Cyclosporin had been forbidden for clinical use in patients under 18 years of age, but by agreement with the drug company and the Food and Drug Administration, we were empowered to do the first trials with this agent in pediatric patients. These were liver as well as kidney recipients whose sera contained such widely reacting T-warm cytotoxic antibodies that they were considered untreatable under conventional circumstances. With this experience, we now realize that the supreme value of cyclosporin A will be for pediatric patients whose growth and development no doubt would be impeded by chronic high dose steroid therapy.

We entered 14 patients into a potential cyclosporin trial. Two of these patients died on the operating table. Of the 12 patients who could be treated with cyclosporin and low-dose steroids, only 1 failed to survive the first postoperative year. The 1-year survival of those actually treated was 92% (9). Even including the two unfortunate operative deaths, the 1-year survival of the liver recipients was almost 80%. These results were better than our entire historical experience with liver transplantation using standard immunosuppression (Fig. 1).

Since arriving in Pittsburgh, we have treated an additional 21 patients. These patients, combined with the 14 earlier Colorado cases, give us 34. The indications for operation are listed in Table 4. Of the 34 cases, there were 22 adults, 14 of whom are still alive. There were 12 pediatric cases, of whom 10 are alive (Table 5). The only deaths in this group were due to technical problems. One of the two patients, a child with Byler's syndrome, had a hepatic artery thrombosis. The

Table 4 Liver Transplantation in the Cyclosporin Era: 1980–1981

Chronic active hepatitis	8
Primary hepatic malignancy (three hepatoma, one Klatskin)	4
Biliary atresia	4
α_1-Antitrypsin deficiency	4
Budd-Chiari syndrome	3
Secondary biliary cirrhosis	3
Primary biliary cirrhosis	2
Sclerosing cholangitis (one with duct cell carcinoma)	2
Congenital hepatic fibrosis	2
Byler's syndrome	1
Wilson's disease	1
Total	34

other death was in a child with α_1-antitrypsin deficiency. His choledochojejunostomy anastomosis apparently leaked, creating an abscess which eroded into the portal vein.

In children with biliary atresia, four of four survive, the longest follow-up being well over a year (Table 5).

In the pediatric cases, 83% of all children treated with cyclosporin are living, going back almost 2 years. The results make it look as if a new era has arrived in liver transplantation.

Editors' note: The evolution of liver transplantation, issues evolved and the most recent survival data have been updated since this symposium (1).

Table 5 Pediatric Cases of Liver Transplantation in the Cyclosporin Era

	Number	Alive[a]
Biliary atresia	4	4
α_1-Antitrypsin	3	2
Congenital hepatic fibrosis	1	1
Neonatal hepatitis	1	1
Wilson's disease	1	1
Budd-Chiari syndrome	1	1
Byler's syndrome	1	0
Total	12	10

[a]Follow-up after 1–15 months. The deaths were caused by (1) hepatic artery thrombosis and (2) biliary anastomosis leak and abscess.

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