In: Orthotopic Liver Transplantation (Gips CH and Krom RAF, Eds.). Martinus Nijhoff Publishers, The Hague, The Netherlands, 1984.

#588

ORIGINAL

(Symposium on liver transplantation at Groningen, The Netherlands, May 19, 1983)

PEDIATRIC LIVER TRANSPLANTATION

Shunzaburo Iwatsuki, M.D.

Thomas E. Starzl, M.D., Ph.D.

Byers W. Shaw, Jr., M.D.

J. Carlton Gartner, M.D.

Basil J. Zitelli, M.D.

J. Jeffrey Malatack, M.D.

From the Department of Surgery, University Health Center of Pittsburgh, University of Pittsburgh, Pittsburgh, Pennsylvania, and Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania.

Reprint requests should be sent to: Shunzaburo Iwatsuki, M.D., Department of Surgery, University Health Center of Pittsburgh, 1084 Scaife Hall, Pittsburgh, PA 15261.

Supported by research grants from the Veterans Administration, National Institutes of Health Bethesda, Grant No AM29961.

The value of cadaveric organ transplantation in infants and children has been often questioned because of the unsatisfactory survival and high morbidity associated with the conventional immunosuppressive regimen which includes azathioprine and prednisone, with or without antilymphocyte globulin. Even after so-called "successful" transplantation the quality of life has been degraded too often by the side effects of high-dose steroid therapy, such as Cushingoid changes, growth retardation and osteoporosis.

Despite the continued efforts over the last twenty years to improve the survival and the quality of life after organ transplantation, real progress had to await the discovery (1, 2) and clinical use (3-6) of cyclosporine, a potent immunosuppressive agent derived from the fungi Cyclidrocarpon lucidum and Trichoderm polysporum.

We are reporting here the progress of liver transplantation in infants and children comparing the results obtained by using a regimen of cyclosporine and low dose steroids to those obtained in the past with the use of conventional immunosuppressive therapy.

CASE MATERIALS AND METHODS

Since the first human orthotopic liver transplantation on March 1, 1963, 296 patients with various diseases have received liver homografts as of April 30 1983 at the University of Colorado and the University of Pittsburgh. Of those 296 recipients, 170 were treated before March, 1980 with conventional double or triple drug therapy, including azathioprine (or cyclophosphamide), prednisone and antilymphocyte globulin. The remaining 126 were transplanted since March, 1980, and were treated with cyclosporine and low dose prednisone. Among the 170 patients given conventional immunosuppression therapy, 86 were pediatric recipients under age 18. Of 100 consecutive liver graft recipients under cyclosporine-low dose steroid therapy since March, 1980 there were

40 pediatric recipients under age 18. The experiences obtained from the total of these 126 pediatric liver recipients form the basis of this report.

Age Distribution

The age distribution of the 86 pediatric recipients under conventional therapy and the 40 patients under cyclosporine therapy is shown in Figure 1. Seventy-four recipients were younger than 6 years old, 29 were between 6 and 12 years old and 23 were older than 12 years old.

Indications for Liver Transplantation

The main indications for liver transplantation in 126 pediatric orthotopic liver recipients are shown in Table 1. Biliary atresia or hypoplasia accounted for over one half of the total pediatric liver transplantations and was the most common diagnosis. The second most common indication was an inborn error of metabolism, such as alph-1-antitrypsin deficiency disease, Wilson's disease, tyrosinemia, glycogen storage disease, and sea blue histiocyte syndrome.

Primary liver malignancy which could not be treated by partial hepatic resection once was thought to be an ideal indication for orthotopic liver transplantation. However, previous experiences (7-12) indicated that malignant tumor recurred in most cases if the malignancy was diagnosed before transplantation and was the major indication for transplantation. On the other hand, if the malignancy was an incidental finding, whether known in advance or found only after examination of the removed specimen, or the malignancy is confined wholly to the liver, cure could be achieved by an orthotopic hepatic transplantation. Ten pediatric patients with primary hepatic malignancy (9 hepatomas and 1 hepatoblastoma) have received liver grafts. In three of them a malignant tumor was the main indication for transplantation but it was an incidental finding in the remaining seven. Of the seven pa-

tients with incidental malignancies, three were among 71 recipients with biliary atresia, two were patients with tyrosinemia, one a patient with alpha-1-antitrypsin deficiency disease and one patient with sea-blue histiocyte syndrome (Table 1, Foot-note).

Immunosuppressive Therapy

The conventional method of immunosuppression, involving the combination of azathioprine and prednisone with or without antilymphocyte globulin (7-9, 13-15) or the substitution of cyclophosphamide (16) for azathioprine, had been reported extensively and in detail elsewhere.

Since March, 1980, combination immunosuppressive therapy with cyclosporine and low-dose prednisone has been used in all liver transplantations (12, 17, 18). Cyclosporine is administered before liver grafting in an oral dose of 17.5 mg/kg or an intravenous dose of 5 to 6 mg/kg. Soon after the operation cyclosporine is given intravenously as a dose of 5 to 6 mg/kg/day in 2 to 3 divided doses. When the patient can resume oral intake, 17.5 mg/kg/day of cyclosporine in two divided doses is given and intravenous doses are gradually withdrawn, depending upon the renal function, graft function and blood level of cyclosporine. Maintenance doses of cyclosporine are adjusted mainly on the nephrotoxicity of the drug. Usually the dose is in the 12 mg/kg/day range at one month and 10 mg/kg/day at six months in pediatric recipients. Infants and younger children seem to tolerate the drug better than older children and adults.

Steroids are a necessary addition to cyclosporine to achieve adequate immunosuppression, but the doses used are much less than those required in combination with azathioprine. Soon after revascularization of the liver, graft recipients receive 250 or 500 mg of intravenous methylprednisolone

succinate, with those recipients weighing more than 20-30 Kg usually receiving the higher dose.

Postoperatively, the daily dose of methylprednisolone or prednisone is tapered by 20 mg daily, from 100 mg daily on the first day down to a maintenance dose of 10 mg on the sixth day. Further reduction of the steroids dose depends upon graft function. Usually the children are discharged with a maintenance dose of prednisone of 5 mg/day one to two months after transplantation. Initial and maintenance doses of steroids are reduced in infants and smaller children, and are increased in larger children.

If rejection occurs despite the above outlined immunosuppressive therapy, boluses of intravenous steroid therapy and/or a recycle of the original 5-day burst of prednisone therapy are given immediately. Although cyclosporine does not permit much dose manEUverability, it is often possible in infants and children to increase the dose with little risk of nephrotoxicity.

If severe nephrotoxicity was suspected, cyclosporine doses were reduced or the drug was substituted by azathioprine, often with rapid reversal of acute renal failure. The dose of cyclosporine was also reduced in the face of severe infectious complications.

Donor Operation

The liver, heart and kidneys can be procured from a single donor without compromising the anatomy and function of any of the organs. The technique of multiple organ procurement and the early functions of each organ graft have been reported (19, 20). The incidence of first week dialysis in patients receiving renal allografts procured in combination with livers and hearts or both is less than 15%. In addition satisfactory livers and hearts usually can be obtained unless there has been faulty donor selection.

The techniques of donor hepatectomy in children are essentially the same as those in adults (7, 19). However, it is advisable in pediatric liver donors to obtain the celiac axis in continuity with the upper abdominal and thoracic aorta and use the latter for anastomosis with the recipients lower abdominal aorta if it is necessary. If the hepatic graft receives an additional blood supply from the superior mesenteric artery, both the celiac axis and the superior mesenteric artery can be obtained in continuity with the upper abdominal and thoracic aorta, particularly in an infant or small child donor (20).

Recipient Operation

The techniques of orthotopic liver transplantation had been established more than 15 years ago (7) and several minor modifications have been reported (8, 21-24).

In children a bilateral subcostal incision or upper abdominal transverse incision using a previous incision almost always gives an adequate exposure. Recipient hepatectomy in children is usually easier than that in adults.

The most important area wherein pediatric hepatic transplants require particular attention to detail is in the performance of the vascular anastomosis. We employ a continuous suture using monofilament polypropylene for all vascular anastomoses. To avoid the purse stringing which can easily occur with this technique, care is taken to prevent undue traction upon the sutures. Nevertheless, a "growth factor" technique, described elsewhere in detail (24) is left in all vascular suture lines, particularly the arterial and portal vein anastomoses. Every effort should be directed toward eliminating strictures in these suture lines so that turbulent flow and pressure gradients are minimized across the anastomoses.

The order of anastomoses can vary following completion of the suprahepatic vena cava connection. Most commonly the infrahepatic vena cava anastomosis is made next followed by the portal vein, followed by release of the flow through the latter, the lower and upper vena cava channels. The arterial anastomosis is then completed while the liver is perfused by portal vein flow.

In the face of cardiodynamic instability caused by vena caval interruption, or if portal vein clamping appears to be causing undue damage to the intestine the portal vein anastomosis can be done following the upper vena cava and flow through the liver restored with the infrahepatic vena caval ends clamped. The latter can then be reconnected as the third anastomosis.

In addition, one may wish to complete the arterial anastomosis before the portal vein if portal vein flow appears to be inadequate, as may be the case, for example, in some biliary atresia patients with small, sclerotic native portal veins. Finally, all four vascular anastomoses often can be completed in less than 60 - 70 minutes and arterial and portal vein flow restored to the hepatic graft simultaneously.

Bile duct reconstruction methods in pediatric cases are similar to those in adults (7, 25, 26). End-to-end choledochocholedochostomy with a T-tube stent is used whenever recipient anatomy and size permit. In-dwelling internal stents are often necessary for very small bile ducts. In cases of biliary atresia and other bile duct disorders a satisfactory native bile duct is not available and end-to-side anastomosis of graft common duct to a Roux-en-Y loop of jejunum is employed. These also are stented internally.

Cholecystojejunostomy or other methods which depend entirely upon drainage via the cystic duct are now avoided entirely because of the high incidence of obstruction of the cystic duct by sludge in transplanted livers which undergo even minor rejection episodes (25, 27). Operative cholangiograms

through either a T-tube or the graft cystic duct stump are performed to document duct anatomy, patency and competency.

RESULTS

Causes of Death

Fifty-three of the 86 pediatric liver recipients between 1963 and 1980 (precyclosporine era) and 14 of the 40 between 1980 and 1982 (cyclosporine era) died within a year after transplantation. Detailed clinical-pathologic analyses of almost all of these deaths has been reported, using OT code numbers (7-9, 12, 28). Although the causes of deaths in these patients were usually multiple, they were categorized to the best of our knowledge as shown in Table 2.

During the precyclosporine era bacterial, fungal and viral infections were the main cause of deaths within a year after transplantation (20 of 53 deaths). There were 9 deaths from abdominal sepsis, 5 deaths from viral infection (adenovirus, chickenpox and herpes), 4 deaths from systemic bacterial and fungal sepsis and 2 deaths from pulmonary infection. Although infectious complications continue to be a major threat to life after transplantation none of the 14 deaths under cyclosporine therapy was categorized death from infection.

Significant numbers of deaths were caused by surgical technical complications of arterial, venous or biliary anastomoses. In the precyclosporine era there were 15 deaths in this category. Eight of the 15 were failures in biliary duct reconstruction, 4 in hepatic artery anastomosis, 2 in portal venous anastomosis and 1 in suprahepatic inferior vena caval anastomosis. In the cyclosporine era surgical technical complications were the direct cause of death in 7 of the 14 children. There were 3 failures in hepatic artery anastomoses, and one each in both the hepatic artery and portal vein anastomosis,

portal venous anastomosis, suprahepatic vena caval anastomosis, and biliary duct reconstruction.

Acute and chronic graft rejection were the third main cause of death in the precyclosporine era and the second in the cyclosporine era. Despite the better immunosuppression therapy and the improved survival with cyclosporine approximately 10 per cent of the recipients died from graft rejection both in the precyclosporine era and in the cyclosporine era.

Survival

One Year Survival:

Actual survival of 86 pediatric liver recipients in the precyclosporine era and actuarial survival of 40 pediatric recipients in the cyclosporine era are shown in Figure 2. After the introduction of cyclosporine the one year survival after liver transplantation improved from 40% to 62%.

Age and Survival:

Because the majority of deaths within the first year occurred within three months after liver transplantation the three month survival of each age group is compared in Figure 1. In the precyclosporine era 28 of 53 (53%) infants and preschool children (less than 6 years old), 8 of 16 (50%) school age children (between 6 and 12 years old), and 13 of 17 (76%) adolescents lived more than 3 months. In the cyclosporine era 16 of 21 (76%) infants and preschool children, 8 of 12 (67%) school children and 6 of 7 (86%) adolescents lived more than three months. Both in the precyclosporine era and in the cyclosporine era 3 month survival of infants and preschool children was statistically not different from those of school children. Three month survival of the adolescents was slightly better than those of younger children in both eras.

It is worthwhile to note that 5 of 7 (71%) infants (less than a year old) lived more than three months. The technical difficulties in infant surgery have been fairly well overcome in liver transplantation as well. The age of children should not be a consideration in accepting them as candidates for liver transplantation. Our youngest recipients have been 3 and 6 months.

Liver Disease and Survival:

The influence of original liver disease upon survival was analyzed in the two most common indications (biliary atresia and inborn metabolic errors) of pediatric liver transplantation, and shown in Figures 3 and 4. Both in the precyclosporine era and the cyclosporine era survival of children with inborn metabolic errors was significantly better than those of children with biliary atresia. The survival of children with biliary atresia was lower than overall survival in the precyclosporine era, but it was similar to the overall survival in the cyclosporine era. This improvement in survival of children with biliary atresia may well reflect the better surgical techniques, management and immunosuppression with cyclosporine.

Five Year Survival:

Seventy-five pediatric patients received liver transplantation more than 5 years ago (precyclosporine era). Sixteen of the 75 (21%) lived more than 5 years, and 15 are still alive between 5 and 14 years after transplantation as of April, 1983. All but two have normal liver function and attend school or work full time. Two patients with abnormal liver function lost their jobs recently.

Long term survival data in the cyclosporine era is not available yet, but 13 children are alive and in good health between one and three years after transplantation.

DISCUSSION

Since the introduction of cyclosporine, the results of organ transplantation such as kidney (5, 6, 29), liver (12, 17, 18), and heart (30), have improved significantly.

In combination with a low dose steroid, cyclosporine provides more effective and safer immunosuppression than conventional double or triple drug immunosuppression therapy (azathioprine and prednisone with or without antilymphocyte globulin). In pediatric liver transplantation the one year survival improved from 40% to 62% with cyclosporine and low dose steroid therapy. Infectious complications, which had been the most frequent direct cause of death after liver transplantation with conventional immunosuppression therapy, became less frequent and more treatable under this new immunosuppression therapy. Children can grow at a normal or better rate after transplantation and complications of high dose steroids such as Cushingoid feature and osteopathy have been virtually eliminated.

The opinion that infants and small children may not be good candidates for liver transplantation because of age and size has been proved incorrect. Survivals of infants and smaller children have been as good as larger children, and survivals of pediatric recipients have been better than those of adults both in the precyclosporine and the cyclosporine era.

The original liver disease has had some influence upon the outcome of transplantation. Children with liver-based inborn metabolic errors have done better than those with biliary atresia or hypoplasia. This is partly due to the fact that previous major surgeries such as Kasai operation (for biliary atresia) make the transplantation operation more difficult; anatomic anomalies have been an additional factor. However, in the cyclosporine era the results of liver transplantation for biliary atresia has raised to the level of over-

all survivals of pediatric cases, but it is till inferior to that after treatment of inborn metabolic errors.

Survival and quality of life after liver transplantation have improved significantly since the introduction of cyclosporine, and it has become a reliable method of therapy for otherwise untreatable liver diseases. As the experience in pediatric liver transplantation expands and deepens, further improvement of outcomes and better understanding of various liver disease can be expected.

REFERENCES

1. Borel JF, Feurer C, Gubler HU, Stahelin H. Biological effects of cyclosporin A; a new antilymphocytic agent. Agents Actions 1976;6:468-75.

2. Borel JF, Feurer C, Magnee C, Stahelin H. Effects of the new antilymphocytic peptide cyclosporin A in animals. Immunology 1977;32:1017-25.

3. Calne RY, White DJG, Thiru S, Evans DB, McMaster P, Dunn DC. Cyclosporin A in patients receiving renal allografts from cadaver donors. Lancet 1978;2:1323-27.

4. Calne RY, Rolles K, White DJG, Thiru S, Evans DB, McMaster P, Dunn DC, Craddock GN, Henderson RG, Aziz S, Lewis P. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs; 32 kidneys, 2 pancreases, 2 livers. Lancet 1979;2:1033-36.

5. Starzl TE, Weil R III, Iwatsuki S, Klintmalm GBG, Schroter GP, Koep LJ, Iwaki Y, Teraskai PI, Porter KA. The use of cyclosporin A and prednisone in cadaveric kidney transplantation. Surg Gynecol Obstet 1980;151:17-26.

6. Starzl TE, Klintmalm GBG, Weil R III, Porter KA, Iwatsuki S, Schroter GP, Fernandez-Bueno C, MacHugh N. Cyclosporin A and steroid therapy in 66 cadaver kidney recipients. Surg Gynecol Obstet 1981;153:486-94.

7. Starzl TE, (With the assistance of CW Putnam). Experience in Hepatic Transplantation. Philadelphia: WB Saunders, 1969.

8. Starzl TE, Porter KA, Putnam CW, Schroter GPJ, Halgrimson CG, Weil R III, Hoelscher M, Reid HAS. Orthotopic liver transplantation in 93 patients. Surg Gynecol Obstet 1976;142:487-505.

9. Starzl TE, Koep LJ, Halgrimson CG, Hood J, Schroter GPJ, Porter KA, Weil R III. Fifteen years of clinical liver transplantation. Gastroenterology 1979;77:375-88.

10. Iwatsuki S, Klintmalm GBG, Starzl TE. Total hepatectomy and liver replacement (Orthotopic liver transplantation) for primary hepatic malignancy. World J Surg 1982;6:81-85.

11. Calne RY. Liver transplantation for liver cancer. World J Surg 1982;6:76-80.

12. Starzl TE, Iwatsuki S, Van Thiel DH, Gartner JC, Zitelli BJ, Malatack JJ, Schade RR, Shaw BW Jr, Hakala TR, Rosenthal JT, Porter KA. Evolution of liver transplantation. Hepatology 1982;2:614-36.

13. Starzl TE, Marchioro TL, Huntley RT, Rifkind D, Rowlands DT Jr, Dickinson TC, Waddell WR. Experimental and clinical homotransplantation of the liver. Ann N Y Acad Sci 1964;120:739-65.

14. Starzl TE, Marchioro TL, Faris TD, McCardle RJ, Iwasaki Y. Avenues of future research in homotransplantation of the liver: With particular reference to hepatic supportive procedures, antilymphocyte serum, and tissue typing. Am J Surg 1966;112:391-400.

15. Starzl TE. Experience in Renal Transplantation. Philadephia: WB Saunders, 1964.

16. Starzl TE, Putnam CW, Halgrimson CG, Schroter GP, Martineau G, Launois B, Corman JL, Penn I, Booth AS Jr, Porter KA, Groth CG. Cyclophosphamide and whole organ transplantation in humans. Surg Gynecol Obstet 1971;133:981-99.

17. Starzl TE, Iwatsuki S, Klintmalm GBG, Schroter GPJ, Weil R III, Koep LJ, Porter KA. Liver transplantation, 1980, with particular reference to Cyclosporin A. Transplant Proc 1981;13:281-85.

18. Starzl TE, Klintmalm GBG, Porter KA, Iwatsuki S, Schroter GP. Liver transplantation with use of Cyclosporin A and prednisone. N Engl J Med 1981;305:266-69.

19. Shaw BW Jr, Hakala T, Rosenthal JT, Iwatsuki S, Broznick B, Starzl TE. Combination donor hepatectomy and nephrectomy and early functional results of allografts. Surg Gynecol Obstet 1982;155:321-325.

20. Shaw BW Jr, Rosenthal JT, Griffith BF, Hardesty RL, Broznik B, Hakala T, Bahnson HT, Starzl TE. Techniques for combined procurement of hearts and kidneys with satisfactory early function of renal allografts. Surg Gynecol Obstet (in press).

21. Shaw BW Jr, Iwatsuki S, and Starzl TE. Alternative methods of hepatic graft arterialization. Surg Gynecol Obstet (in press).

22. Starzl TE, Koep LJ, Weil R III, Halgrimson CG. Development of a supra-hepatic recipient vena cava cuff for liver transplantation. Surg Gynecol Obstet 1979;149:76-77.

23. Starzl TE, Groth CG, Brettschneider L. An everting technique for intra-luminal vascular suturing. Surg Gynecol Obstet 1968;127:125-26.

24. Starzl TE, Iwatsuki S, Shaw BW Jr. A "Growth Factor" in fine vascular anastomoses. Surg Gynecol Obstet (in press).

25. Starzl TE, Putnam CW, Hansbrough JF, Porter KA, Reid HAS. Biliary complications after liver transplantation; with special reference to the biliary cast syndrome and techniques of secondary duct repair. Surgery 1976;81:212-21.

26. Iwatsuki S, Shaw BW Jr, Starzl TE. Biliary tract complications in liver transplantation under cyclosporine-steroid therapy. Transplant Proc 1983;15:1288-91.

27. Martineau G, Porter KA, Corman J, Launois B, Schroter G, Palmer W, Putnam CW, Groth CG, Halgrimson CG, Penn I, Starzl TE. Delayed biliary duct obstruction after orthotopic liver transplantation. Surgery 1972;72:604-10.

28. Starzl TE, Koep LJ, Porter KA, Schroter GPJ, Weil R III, Hartley RB, Halgrimson CG. Decline in survival after liver transplantation. Arch Surg 1980;115:815-19.

29. Starzl TE, Hakala TR, Rosenthal JT, Iwatsuki S, Shaw BW Jr. Variable convalescence and therapy after cadaveric renal transplantations under cyclosporin A and steroids. Surg Gynecol Obstet 1982;154:819-25.

30. Shumway NE. Recent advances in cardiac transplantation. Transplant Proc 1983;15:1221-24.

FIGURES

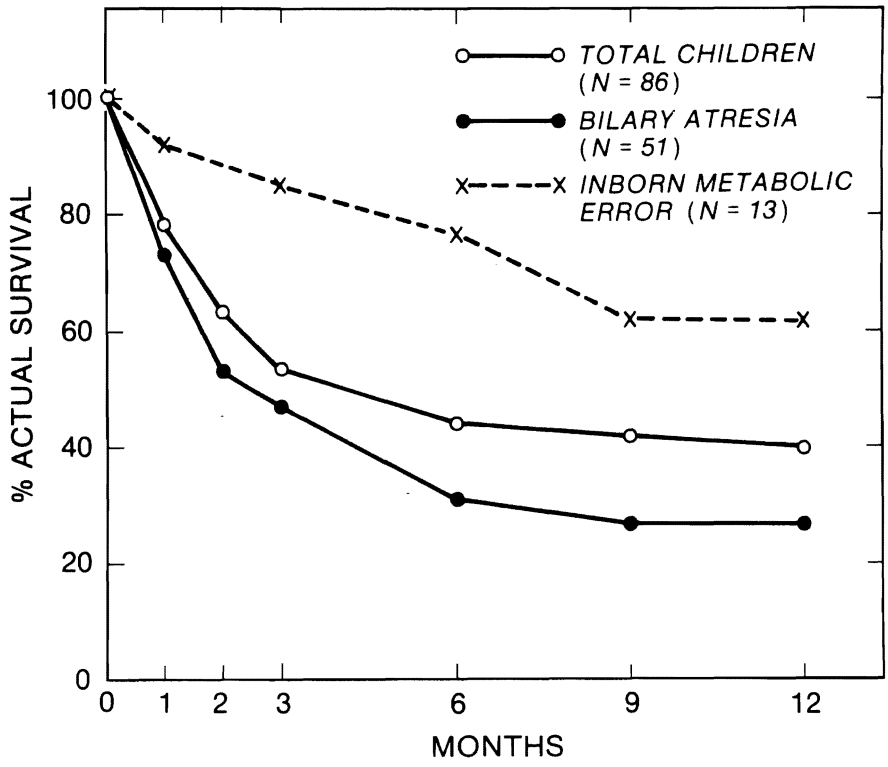
Figure 1. Age distribution of 126 pediatric liver recipients. A shaded square represents a child who survived more than 3 months, and a black square represents a child who died within 3 months.

Figure 2. A comparison of survival after liver transplantation between 86 pediatric liver recipients under conventional immunosuppression therapy (azthioprine, prednisone and ALG) and 40 pediatric recipients under cyclosporine-prednisone therapy.

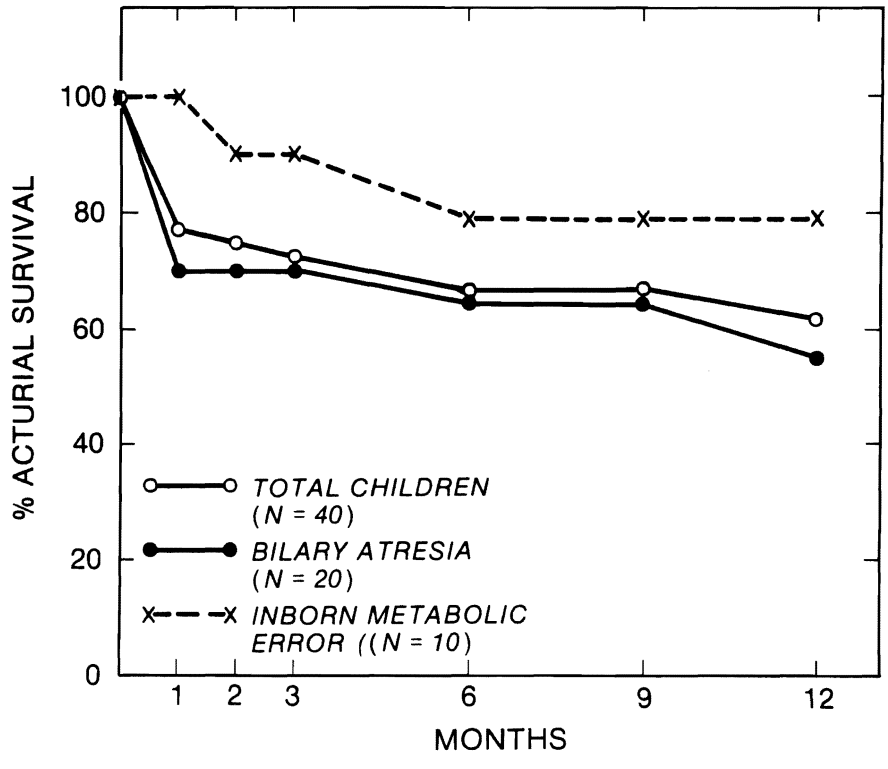
Figure 3. Influence of original liver disease upon one year survival under conventional immunosuppression therapy.

Figure 4. Influence of original liver disease upon one year survival under cyclosporine-steroid therapy.

PEDIATRIC LIVER TRANSPLANTATION: PRE-CYCLOSPORINE ERA



PEDIATRIC LIVER TRANSPLANTATION: CYCLOSPORINE ERA



AGE DISTRIBUTION OF PEDIATRIC LIVER RECIPIENTS