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Selective Surgical Management of Progressive Familial Intrahepatic Cholestasis (Byler's Disease)

By Jean C. Emond and Peter F. Whitington
San Francisco, California and Chicago, Illinois

• **Progressive familial intrahepatic cholestasis (PFIC) presents in early childhood with pruritus, jaundice, hepatomegaly, and growth failure. Medical therapy is unsuccessful, with progression from cholestasis to hepatic fibrosis, cirrhosis, and ultimately death before the age of 10 years. Because of evidence that biliary diversion can arrest or reverse progression to hepatic fibrosis, we have used partial biliary diversion (PBD) as primary therapy in PFIC, reserving orthotopic liver transplantation (OLT) for children who have progressive disease or established cirrhosis. Seventeen children with PFIC (aged 2 months to 19 years) have been treated. PBD was performed in eight cases. In these procedures, a 10-cm properistaltic jejunal segment was anastomosed to the side of the gallbladder, terminating as an end stoma for the collection and discard of bile. Eleven patients with hepatic insufficiency (or end-stage cirrhosis) received OLT using standard techniques, at the average age of 4 years. Six of the eight children treated with PBD had complete resolution of clinical symptoms and remain well 1 to 13 years postoperatively. These six patients have conjugated bilirubin values of less than 0.3 mg/dL, normal transaminases, and a serum bile salt concentration of less than 10 nmol/mL. All have had either reversal or no progression of the hepatic fibrosis. Postoperative bleeding complications occurred in two (25%), which required reoperation. One patient had an adhesive intestinal obstruction that was managed surgically 9 months postoperatively. Two patients had no benefit from PBD, and all of them had severe bridging fibrosis (1) or cirrhosis (3). These and nine others with cirrhosis at the time of presentation received orthotopic liver transplantation; of these, eight are alive (1 to 5 years postoperatively). These results show the importance of establishing a correct diagnosis in children with cholestasis. Clinical symptoms often are severe in children with PFIC before the development of irreversible hepatic fibrosis. Because several patients who appear to have been cured with PBD initially were scheduled for OLT, it is important that transplant surgeons recognize the feasibility of this approach.**

INDEX WORDS: Byler's disease, intrahepatic cholestasis.

PROGRESSIVE familial intrahepatic cholestasis (PFIC) is a progressive cholestatic liver disease of childhood.[1,2] Clayton et al described the disorder in a large Amish kindred, descended from Jacob Byler, and the term "Byler's disease" often has been used to describe the condition.[3,4] Typical clinical findings include jaundice, itching, and growth failure, and most cases present in the first 6 months of life. The pattern of occurrence is consistent with a Mendelian autosomal-recessive inheritance. Low serum g-glutamyl transpeptidase (GGTP) differentiates PFIC from other chronic cholestatic diseases in children. In our reported series of patients, serum GGTP values were at least one log order lower than those of patients with other common cholestatic diseases.[1] These patients also have relatively normal serum cholesterol levels, which are significantly lower than in other forms of pediatric cholestatic liver disease. Patients with the disease have severely diminished quality of life, secondary to their unusually severe pruritus, delayed growth, and development; without specific therapy they usually die during the first decade of life from complications of progressively worsening liver disease.

Cases of PFIC generally are refractory to medical therapy. Approaches that have been used include the administration of choleretic agents (phenobarbital and ursodeoxycholic acid[5]), cholestyramine, or colestipol (to bind bile acids in the intestinal lumen), rifampin,[6] antihistamines, carbamazepine, UV-B light therapy, and plasmapheresis.[7] Of the 33 patients in our series, only three with relatively mild disease are alive at 6 to 7 years of age, and they receive only medical support. In contrast, 23 of the 26 patients who had surgery are alive and well.[1]

From the Liver Transplant Program, University of California, San Francisco, CA, and the Department of Pediatrics, University of Chicago, Chicago, IL.

Address reprint requests to Jean C. Emond, MD, Liver Transplant Program, University of California, San Francisco, 505 Parnassus Ave (M-896), San Francisco, CA 94143-0780.

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Orthotopic liver transplantation (OLT) has been used in the management of PFIC. PFIC is among the five most common disease indications for OLT in some series.[8,9] OLT as the primary approach to PFIC results in cure, but at the expense of surgical risk and a commitment to a lifetime of immunosuppressive therapy.[10] Because of the concept that PFIC results from a transport defect that causes retention of bile salts and secondary toxic hepatocyte injury, surgical strategies to divert bile from the intestine and, therefore, reduce bile acid preload have been proposed, and have been implemented successfully by Whitington et al.[1,11,12] External diversion of gallbladder bile, by either cholecystostomy or use of an interposition jejunal conduit, has been the most successful method, although jejuno-ileal bypass, which also interrupts the enterohepatic recirculation of bile salts, also has been successful in two patients.[1,12] These treatments have reversed clinical symptomotology and arrested histological hepatic injury in patients with PFIC.[12]

In this report we present our experience with the management of 17 children with PFIC and propose a therapeutic algorithm in which partial biliary diversion (PBD) is used as primary therapy. Liver transplantation should be reserved for patients who have established cirrhosis at the time of presentation or who have progressive liver disease despite biliary diversion.

MATERIALS AND METHODS

The records of 17 patients with PFIC who were treated at the University of Chicago between 1985 and 1991 were reviewed. Upon referral, patients underwent a complete evaluation, including liver biopsy. Staging of liver disease was performed to determine candidacy for surgical therapy. Patients without immediate need for liver transplantation received a trial of medical therapy (with ursodeoxycolic acid), but clinical symptomatology did not improve. Each patient had at least one form of surgical treatment, which included open biopsy with cholecystostomy (3), partial biliary drainage (8), and liver transplantation (11). The decision between cholecystectomy and partial biliary drainage was made according to the condition of the patient at the time of evaluation. Patients with advanced disease and thus little likelihood of having long-term benefit from biliary diversion were treated with cholecystectomy to determine if bile diversion would improve their clinical condition. If it did, permanent drainage would be performed later. Liver transplantation was performed as primary therapy only in patients with clearly advanced cirrhosis. Complete follow-up was available for 2 to 6 years after treatment.

Surgical Techniques

Cholecystostomy is performed using a right-upper-quadrant transverse incision, with inspection of the liver and a biopsy. The exit site for the tube is in the right upper quadrant. PBD (Fig 1) is performed using a similar incision. After the biopsy and liver inspection, the proximal jejunum is divided 15 cm from the ligament of Treitz. A segment of intestine 10 cm long is isolated for use as the biliary conduit with end-to-end reconstruction of the

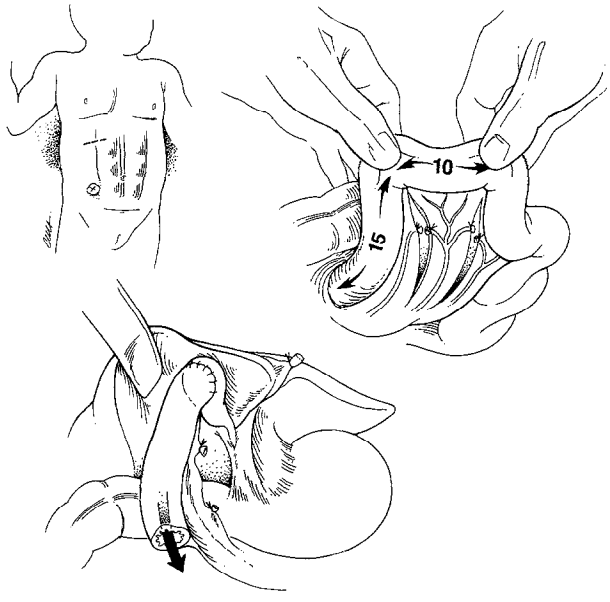

Fig 1. The procedure of partial biliary diversion is depicted schematically. Division of the proximal 15 cm distal to the ligament of Treitz jejunum permits the creation of a 10-cm jejunal conduit to deliver gallbladder bile to the exterior. Insert shows the position of the external stoma.

continuity of the bowel. The conduit is placed in an antecolic orientation, and end-to-end anastomosis is made between the proximal portion of the conduit and the most dependent portion of the gallbladder. The distal end of the conduit is matured as a standard Brooke-type ostomy in the right lower quadrant. Preoperative planning of the location of the stoma is important to avoid interference with the belt line, which is a problem in small children who have a protuberant abdomen. Liver transplantation was performed according to standard techniques.

Management and Data Collection

Patients received standard postoperative care after the surgical procedures, including perioperative antibiotic prophylaxis (using second-generation cephalosporins) and nasogastric decompression for 24 to 72 hours. Those whose conditions responded to PBD were discharged from the hospital in 5 to 7 days. Serum bilirubin and total serum bile salt concentrations were measured regularly to document the effect of the procedure. Ursodeoxycholic acid therapy (15 to 20 mg/kg/d) was continued postoperatively in two patients whose condition did not respond initially to biliary diversion. Patients who had liver transplantation were managed according to standard protocols in our institution and received immunosuppression based on cyclosporine.[13] Data are presented as mean ± standard deviation or range. Differences between population means were tested for significance using the Student's *t* test. A *P* value of less than .05 was considered significant.

RESULTS

Choice of Therapy for Treated Patients

Eleven patients received liver transplantation; nine of them had immediate indications for transplantation, and two did not respond to PBD. All three patients who initially underwent cholecystostomy had conversion to permanent external biliary drainage

because of the initial method's success in lowering the serum bile salt concentration. One patient received cholecystostomy followed by external partial biliary drainage and subsequent liver transplantation because of progressive liver disease. Another patient had PBD followed by transplantation. The interval between PBD and transplantation for these two patients was 3 weeks and 7 months, respectively.

Clinical Characteristics of Patients at the Time of Treatment

Tables 1 and 2 summarize the clinical characteristics and laboratory data of the patients at the time of treatment. Patients who had successful bile diversion (n = 6) and are compared with those who required liver transplantation (n = 11). In general, those with successful PBD were older (10.5 *v* 4.6 years (P = .04). All patients had grade 3 or 4 pruritus[11] and growth failure, and were below the fifth percentile for height at the time of presentation. Of the patients who had successful diversion, none had histological cirrhosis at the time of presentation. Two patients who initially were treated with PBD and subsequently required transplantation had histological cirrhosis, but without complications such as coagulopathy, portal hypertension, or ascites. Laboratory data are presented in Table 2. In general, patients who had transplantation had more severe cholestasis and lower levels of aminotranferase; however, the differences were not significant. Serum prothrombin time was prolonged in patients who had primary transplantation, and the serum albumin level was significantly lower in these patients.

Cholecystostomy performed in three patients was associated with early postoperative bleeding; in one case this required a second surgical procedure. Dislodgment of the tubes occurred in two patients. One patient, a 4 year old, had an infection of the tube tract. It was generally difficult to satisfactorily maintain the tubes in children for more than a few weeks. Of the patients with PBD (n = 8), one had hemoperitoneum that required exploration. Two patients had stomal herniation. One of them remained asymptomatic and was managed without surgery, and the other had intestinal obstruction that necessitated emergency surgery. This was formally repaired 3 years after the initial operation.

Table 1. Clinical Characteristics of Patients at Time of Treatment: Patients With PBD Versus OLT

Observation	PBD (n = 6)	OLT (n = 11)	*P* Value*
Age (yr)	10.5 ± 7.1	4.6 ± 3.4	.04
Pruritus (grade 3 or 4)	100%	100%	
Growth failure (< 5%)	100%	100%	
Hepatomegaly	100%	100%	
Histological cirrhosis	0	100%	

*Unpaired Student's *t* test.

Table 2. Laboratory Profiles of Patients at Time of Treatment: PBD Versus OLT

Observation	PBD (n = 6)	OLT (n = 11)	*P* Value*
Bilirubin (mg/dL)	6.5 ± 2.4	12.8 ± 6.5	.04
ALT (IU/L)	226 ± 283	171 ± 125	.58
GGT (IU/L)	30 ± 15	39 ± 19	.36
Alkaline phosphatase (IU/L)	518 ± 228	452 ± 206	.57
Prothrombin time (s)	13.9 ± 1.3	16.2 ± 2.9	.09
Albumin		3.4 ± .8	.04

The long-term results of PBD are presented in Table 3. Six of the eight patients had improvement or complete resolution of clinical symptomotology (follow-up period, 2.6 to 5 years). Pruritus resolved in all six, and all six attend school and engage in age-appropriate activities. Catch-up growth has occurred in four of the six, but the other two remain short for their age (below the fifth percentile). Laboratory data have not normalized completely. The serum bilirubin level is elevated in several (mean, 2.5 mg/dL; range, 0.9 to 5.5). The bilirubin fraction is predominantly unconjugated in the patient with the highest serum bilirubin level; she has been diagnosed as having Gilbert's syndrome. Serum alanine aminotransferase (ALT) ranges from 89 to 130 IU/L (mean, 100 IU/L), which suggests there is persistent low-grade hepatocyte injury in these patients. After PBD there is an increase (toward normal) in the level of GGTP, but alkaline phosphatase remains somewhat elevated. Percutaneous liver biopsies in all patients have shown improvement, with resolution of cholestasis and either regression of or no change in fibrosis.

Table 4 shows the results of liver transplantation for PFIC (n = 11). The survival rate is 73% (mean follow-up period, 3.8 years; range, 2 to 6 years). Two of the three deaths occurred early in the postoperative period. In both cases the patients received split-liver transplantation, which was complicated by

Table 3. Long-Term Results for Eight Patients Who Had PBD

Observation	
Clinical response	6 of 8 (follow-up period, 2.3 to 4.9 yr)
Pruritus resolved	6 of 6
Attend school	6 of 6
Persistent growth retardation	2 of 6
Laboratory Data	Mean (range)
Bilirubin level (mg/dL)	2.5 (0.9-5.5)
ALT (IU/L)	100 (89-130)
GGT (IU/L)	85 (33-212)
Alkaline phosphatase (IU/L)	319 (167-415)

NOTE. Clinical and laboratory assessment as of June 1993.

Table 4. Results of Liver Transplantation for PIFC (n = 11)

Observation	Value
Survived	8 of 11 (73%); mean follow-up period, 3.8 yr (1.8-5.6 yr)
Clinically well	8 of 8
Attend school	8 of 8
Growth failure persists	3 of 8
Normal serum bilirubin	8 of 8

surgical difficulties.[14] In the first instance, arterial thrombosis (which required retransplantation) occurred after an initial period of satisfactory graft function. Retransplantation was difficult and was associated with poor graft function, which resulted in death 7 weeks posttransplantation, from multisystem organ failure and sepsis. The second patient underwent liver grafting, with poor initial function complicated by rejection. Rejection therapy did not improve the clinical situation, and retransplantation was performed in the presence of sepsis and hepatic insufficiency. The patient died shortly after the retransplantation. In the third case, the patient died 2 years after liver transplantation, of lymphoproliferative disease that did not respond to therapy. The other eight children remain clinically well; they attend school and have age-appropriate development. All have normal levels of serum bilirubin, but growth failure persists in three of them. The others have experienced catch-up growth and are in the normal range for height and weight.

DISCUSSION

This study shows the efficacy of PBD in selected patients with PFIC and proves that this modality is a positive alternative to liver replacement. Six of our 17 patients have experienced complete clinical remission of the syndrome, without liver transplantation, and appear to have been well served by the procedure. Based on our conceptual framework of the benefits of PBD, this approach has been the centerpiece of management (Fig 2). The long time of accrual of patients in this retrospective study limits the interpretation of our results. Most patients in this series had established cirrhosis at the time of referral and were referred for transplantation, reflecting a lack of awareness of alternative therapy available for patients with PFIC. We did not develop confidence in PBD as primary therapy for PFIC until 1988. After several failures, cholecystostomy was abandoned because of its associated morbidity, the realization that PBD's associated morbidity was no greater, and the documentation of clinical improvement in every case, obviating the need for a "trial" of bile drainage before to the definitive surgical procedure. We currently recommend PBD as initial therapy for all PFIC patients who do not have cirrhosis with complications at the time of presentation. It is our expectation that the overall results of treatment of PFIC will improve, to approximate the 75% success rate of our patients with PBD, as awareness of the benefits of the therapy becomes more widely known.

To institute successful therapy, it is important to promptly establish the diagnosis of PFIC. The clinical presentation is typical and is characterized by pruritus, cholestasis, and growth failure, which develop in the first year of life. A positive family history is often present. Characteristic laboratory findings include elevated levels of serum bilirubin and aminotransferases. In contrast to other cholestatic disorders of childhood, GGTP and serum cholesterol levels are low.[1] The liver biopsy specimen has typical histological features, including parenchymal cholestasis with disruption of liver cell plates and ballooning of hepatocytes, particularly in the central zones. In the portal tracts, duct injury is present which leads to paucity in most patients. However, there is a distinct absence of inflammatory cells in the portal tracts.[2] The presence of typical clinical, biochemical, and histological features, with the exclusion of structural abnormalities of the biliary tract, permits establishment of the diagnosis of PFIC.

PFIC is relatively uncommon (fewer than 100 reported cases), but as a cause of progressive cholestatic disease in children it ranks only behind biliary atresia.[1,15] Curative therapy in the form of PBD or liver replacement has only been fully developed in recent years; most clinical descriptions of PFIC or Byler's disease have been case reports and natural history studies.[3,4,16-27] Some patients referred to our center had had follow-up for many years, with severe symptomatology and progressive liver disease, but

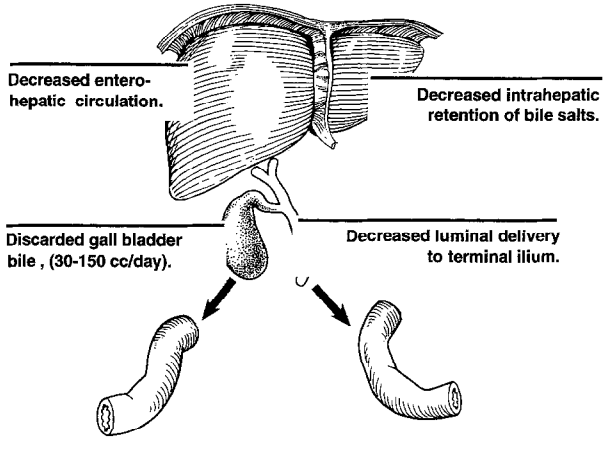

Fig 2. Selective management of PFIC. Conceptual framework supporting partial biliary diversion.

without a diagnosis. Even patients with less severe disease often have associated secondary complications because of fat-soluble vitamin deficiency and delayed sexual maturation, which would be prevented by earlier recognition and intervention. Early recognition of PFIC and its immediate therapy with PBD can, in our opinion, interrupt the natural history of the disease, reduce its complications to an acceptable level, and prevent the need for transplantation in most patients.

Although the genetic defect associated with PFIC has not been determined, it is apparent that the hepatic abnormality is associated with a defect in bile salt transport.[12,28] This leads to an increase in the hepatocyte concentrations of bile salts, which are strong amphiphilic detergents and cause hepatic injury. Further evidence of the validity of this concept is provided by the clinical response of patients who have been treated with PBD. Cholecystostomy with discard of the bile, PBD as we have described it, and jejuno-ileal bypass all result in reduced enterohepatic recirculation for bile salts and reduced demand for the liver to transport them. The fact that this well-documented observation is associated with amelioration of both clinical symptomotology and biochemical parameters of hepatic injury and hepatic histology justifies these therapeutic procedures. Cholecystostomy probably is not indicated for the treatment of these patients because long-term maintenance of an external tube is difficult in children. Ileal bypass has been effective in two patients but has been associated with diarrhea and has not been as satisfactory as PBD (P.F. Whitington, unpublished observations). Therefore it is reserved for treatment of patients who have had previous cholecystectomy, which is common because of the high frequency of gallstones in these patients.[12] Because this choice is suboptimal, cholecystectomy is contraindicated in cases of PFIC.

A number of surgical alternatives that lower bile salts have been proposed. Direct anastomosis of the gallbladder to the skin provides the most direct method of external diversion. We do not have experience with this procedure, but some patients thus treated have had difficulties maintaining an adequately watertight stoma, and have experienced problems with either leakage of the ostomy appliance or skin irritation from bile leakage (D.K. Freese, personal communication). There is also the theoretical concern that direct communication between the gallbladder and the skin, without an intervening segment of peristaltic bowel, might predispose the patients to cholangitis; however, this has not been described. Vacanti (personal communication) used a tube of the gallbladder wall to create a stoma, with good early results in two patients. The jejunal interposition we described has several advantages. First, the optimal placement of the stoma in the right lower quadrant can be afforded by use of a longer interposition. Second, the properistaltic function of the conduit prevents reflux of contaminated bile from the external stoma into the biliary tree and reduces the risk of cholangitis. Third, the construction of this biliary conduit in the same position as that which would be required by Roux-en-Y anastomosis for transplantation makes it possible to readily dismantle this diversion at the time of transplantation if that procedure becomes necessary.

We considered alternative surgical procedures that would avoid the need for a permanent external stoma, which, while representing little real disability for the patient, are a cosmetic concern and thus may impact on lifestyle. Alternative means for eliminating bile include direct anastomosis between the gallbladder and the colon, or the urinary tract, or use of an interposition conduit to achieve the same goal. The deleterious consequences of reflux of urine into the biliary tree or the impact of bile on the epithelium of the urinary bladder are unknown, and animal models might not adequately address the impact of this long-term modification in humans, with the risk of carcinogenesis from chronic mucosal injury or other long-term complications. Harrison (personal communication) has used an interposition appendiceal conduit between the gallbladder and the urinary bladder in one patient with PFIC, but decompression was inadequate. We have grave concerns about any anastomosis between the biliary tract and the colon because of the risk of contamination and cholangitis. It is our present belief that, although not ideal, external diversion using a jejunal conduit is an acceptable compromise for application in these patients long term.

In our analysis of the factors associated with successful response to biliary drainage in this series, it was clear that the presence of advanced cirrhosis precludes a good outcome with PBD. Because this study is retrospective, it is not possible to exclude the possibility that patients whose condition responded to PBD might have a milder form of PFIC. In favor of this argument is the fact that responders were older, with a longer clinical course, which suggests that the disease may be more severe in younger patients. The PFIC syndrome may well encompass distinct genetic errors of varying severity. Nonetheless, two of our successfully treated patients were under 3 years of age, and we believe that earlier treatment could result in a 75% success rate. Because our approach to therapy evolved during the study, it is difficult to

distinguish the impact of variations in the natural history of the disease from the successful response to therapy. We hypothesize that the liver failure of many of the patients who were referred late and required OLT might have been prevented by early biliary diversion.

Two patients in this series had transplantation after failure of biliary diversion. In both cases, PBD was performed after cirrhosis had been well established and, in retrospect, probably should not have been performed. The presence of the stoma added a modest risk of infection to OLT, but added little to the difficulty of the hepatectomy. Although we found it easier to discard the previous conduit and create a new Roux-en-Y for biliary reconstruction of the transplant, the conduit itself could be used to create a Roux-Y loop. In our experience, a loop of 10 to 15 cm is sufficient to avoid cholangitis after liver transplantation.

Our series included several patients who had innovative transplantation procedures, including reduced-size livers and split-livers. Although use of a reduced-size graft does not confer increased morbidity or mortality,[29-31] split-liver transplantation has been associated with higher morbidity and mortality in our series and others.[14,29] Two of the three deaths among our 11 patients with PFIC were attributable to technical failure of split-liver grafts. Although we have demonstrated that living-related liver transplantation is a highly effective form of therapy, with a 95% success rate,[32,33] we have not had the opportunity to use a living donor for a patient with PFIC. Overall, patients with PFIC are expected to have an extremely good prognosis with liver grafting if they have transplantation before the development of intractable complications of cirrhosis. An additional benefit of the use of PBD is the unmistakable improvement that has occurred in liver transplantation in recent years, and that likely will continue because of the advances in immunotherapy and medical and surgical management. Although the expected half-life of a liver graft was 3 years in 1988, in 1993 the anticipated half-life of a liver graft was 11 years. Even if partial biliary diversion ultimately represents only palliative therapy, it is unquestionable that patients will benefit from having their transplantation procedures delayed so that they can take advantage of future improvements in transplantation.

Based on these promising results, we recommend that PBD be used as soon as the diagnosis is made, in the hope that 75% of patients with PFIC can be treated without liver replacement. Liver replacement should be performed primarily in patients who have cirrhosis at the time of presentation.

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