

The Outcome of the Older (≥ 100 Days) Infant With Biliary Atresia

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Background: There is a detrimental effect of increasing age on the results of the Kasai portoenterostomy for biliary atresia (BA), and some centers routinely advocate primary liver transplantation for the older infant, irrespective of other criteria. This perception that such infants are indeed irretrievable was tested by retrospective analysis.

Methods: All infants who had undergone surgery for BA during the period 1980 through 2000 aged ≥ 100 days were reviewed. Actuarial survival was calculated using 2 end-points (death and transplantation). A retrospective review of their ultrasonography ($n = 12$) and preoperative liver histology ($n = 22$) was also undertaken to ascertain possible predictive criteria.

Results: A total of 422 infants had BA diagnosed during this period, of which 35 (8.2%) were ≥ 100 days at surgery (median [interquartile range], 133 [range, 108 to 180] days). Surgery included portoenterostomy ($n = 26$), hepaticojejunostomy ($n = 7$), and a resection and end-to-end anastomosis ($n = 1$). A laparotomy only was performed in 1. Five- and 10-year actuarial survival rate with native liver was 45% and

40%, respectively. Currently, 12 (35%) patients are alive with their native liver (8 are anicteric), 9 (28%) have undergone transplantation, and 13 have died. Although there were some survival advantages for types 1 or 2 BA and "noncirrhosis" at time of surgery, neither reached statistical significance. Individual histologic features (eg, degrees of fibrosis, giant cell transformation, bile duct destruction) in the retrospective review of available material were not discriminatory. The finding of a "heterogeneous" parenchyma on ultrasonography was predictive of poor outcome but lacked sensitivity.

Conclusions: The potential for reasonable medium-term survival is present in about one third of infants 100 days or older coming to primary corrective surgery. In the absence of accurate discrimination, the authors continue to favor this option rather than subject all to transplant simply on the basis of age.

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INDEX WORDS: Biliary atresia, Kasai portoenterostomy, cirrhosis.

BILIARY ATRESIA (BA) is an obliterative cholangiopathy of unknown etiology affecting about 1 in 15,000 infants. Although most are full term with a normal birth weight and will present early with obvious signs of conjugated jaundice, pale stools, and dark urine, a small proportion will evade early diagnosis and surgery. Because progression of the untreated liver disease leads to hepatic fibrosis and ultimately end-stage biliary cirrhosis, it is not unexpected that these infants would have a bleak outlook.

The Kasai portoenterostomy has been the mainstay of treatment for BA in the United Kingdom for the past 30 years¹⁻³ with a reported rate of early success, defined by clearance of jaundice, in our center, of 60% to 80%.³⁻⁵ The advent of liver transplantation in the 1980s⁶ meant that an alternative therapeutic procedure became available, although initially it was only offered to the older child who had at least established a degree of bile drainage. Increasing confidence with technical variations such as liver reduction and use of living-related donors has allowed progressively smaller recipients, and currently there is no technical barrier to transplantation during infancy with acceptably small morbidity and mortality rates. Nevertheless, our practice has still been to regard portoenterostomy and transplantation as complementary, reserving the latter for failure of the former.

Only exceptionally have we performed a transplant as a primary procedure.

Studies illustrating the detrimental effect of increasing age at initial surgery appeared in the 1970s and 1980s.^{3,7,8} Inevitably, early reports involved relatively small numbers with too much being made of arbitrary cutoff values and ignoring the observation that the older group were invariably composed of a heterogeneous mix of cases, often undergoing surgery at extremes of age. With larger series, both multicenter^{9,10} and single-center,⁴ it became possible to use stratified age groups, the result of which was a "plateau" effect that showed no particular advantage for the younger age groups. For instance, our own study⁴ showed that the detrimental effect of age in terms of survival with a native liver was only seen in infants of greater than 100 days at initial surgery.

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The aim of this study was to analyze that subgroup of infants who were 100 days or older at the time of portoenterostomy, which we define as "late." The predictive value of some preoperative variables, which have been suggested as important, were also studied.

MATERIALS AND METHODS

King's College Hospital, London is the largest pediatric hepatobiliary unit in the United Kingdom and has specialized in the investigation of jaundiced infants and the treatment of BA since 1974. For the purposes of this study, we restricted our review to those infants who had undergone their primary surgery at this center since 1980 to exclude the effect of a "learning curve" in the acquisition of a new technique.

The macroscopic classification of BA was based on that of the Japanese Association of Pediatric Surgeons and defines type I, atresia affecting the common bile duct; type II, atresia affecting the common hepatic duct, and type III, occlusion at the level of the porta hepatis.

Surgery was performed by 2 surgeons using identical techniques. Briefly, this consisted of liver mobilization, a radical dissection and excision of the extrahepatic biliary tree, and portoenterostomy to a 40 cms Roux loop.¹¹ Early in the series, some infants with type 1 or 2 BA underwent a hepaticojejunostomy. No stomas were used during this period. The postoperative medical and nutritional management was reasonably uniform during this 20-year period and included the use of phenobarbitone, cholestyramine, fat-soluble vitamins, and a medium-chain triglyceride milk formula. Ursodeoxycholic acid, but not corticosteroids, have occasionally been used since the 1990s.

A case-note review established those regarded as "cirrhotic" at the time of primary surgery either on the basis of the diagnostic needle biopsy or operative findings. A retrospective review of the original ultrasound scans and available histopathologic material was also undertaken to try and establish ultrasonic and histologic prognostic criteria.

Ultrasonographic Review

All infants had been scanned using either a Dasonics CV400 (Dasonics, Milpitas, CA), Prisma (Dasonics, Paris, France) or Masters (Dasonics, Santa Clara, CA) ultrasound scanner with 5- or 3.5-MHz probes.

The resistance index (RI) of the hepatic artery waveform was calculated for all Doppler scans. Briefly, this is derived by subtracting end diastolic from peak systolic frequency and dividing by peak systolic frequency. We have previously established that a RI ≥ 1 is predictive of rapid deterioration in BA post-Kasai.¹² There are no data, however, on the predictive value of the pre-Kasai RI. The maximum splenic diameter was also recorded as an indirect index of portal hypertension. Again, we have no data on its actual value in assessing infants with BA.

HISTOLOGIC REVIEW

Formalin-fixed tissue stained with H & E and reticulin was reassessed by a single pathologist (BP). Five variables were evaluated using a semiquantitative scoring system and consisted of fibrosis, cholangiolar bile casts, lobular (parenchymal) cholestasis, bile duct destruction, and presence of giant cells. Fibrosis was graded as 0, no fibrosis; 1, mild portal fibrosis; 2, porto-septal; nonbridging fibrosis; 3, bridging fibrosis; and 4, cirrhosis. The

other features were graded as 0, feature absent and 1, 2, and 3 reflecting increasing intensity of the feature.

Data were expressed as medians and range and compared using nonparametric tests (eg, Mann-Whitney U test). Actuarial (Kaplan-Meier) survival curves were plotted using standard statistic software (Arcus Quikstat 1.1) and differences assessed using a log-rank test. Significance was assumed at $P = .05$.

RESULTS

A total of 422 infants had BA diagnosed and underwent confirmatory laparotomy and portoenterostomy or hepaticojejunostomy from January 1980 to December 2000. Within this group there were 35 (21 female) infants (8%) who underwent surgery at ≥ 100 days with a median age at surgery of 133 (range, 100 to 301) days. Four infants (11%) were premature (< 36 weeks). Two (6%) infants had other anomalies compatible with the biliary atresia splenic malformation syndrome.¹³ Twenty-six infants were referred from within the United Kingdom, whereas 9 originated outside.

BA was classified as type I ($n = 7$, 20%), type 2 ($n = 3$, 9%), and type 3 ($n = 25$, 71%). Of the remaining BA infants ($n = 387$) in the series where classification was possible, 368 (95%) were type 3 and 19 (5%) type 1 or 2. The difference in distribution was significant ($P < .001$). One infant with a chromosomal abnormality and other severe cardiac anomalies underwent a diagnostic laparotomy only that showed a Type 3 BA.

Reasons for Treatment Delay

The reasons for the late diagnosis and treatment of BA were ascertained from case-note analysis. We excluded all 9 non-UK infants and 9 UK infants with pertinent missing data. Of the remaining 17 infants, in one the delay was caused by failure of parents to attend any form of health check or seek medical advice about persisting jaundice; in 6 infants, there was a significant delay in referral attributed to their general practitioner, and in 7 infants, the delay was caused by a misdiagnosis in the referring hospital. In the remaining 3 infants who had been referred to our hospital at an earlier stage, the initial diagnostic liver biopsy was not interpreted as BA.

Prognostic Features

Twelve (37%) infants had evidence of a "cirrhotic" liver, diagnosed either on histologic features on the preoperative liver biopsy or from the operative macroscopic findings. An acquired biliary atresia was diagnosed in 2 infants because of an atypical clinical history and operative findings. These have been described previously.¹⁴ Briefly, one was born at 28 weeks' gestation and sustained many complications attributable to prema-

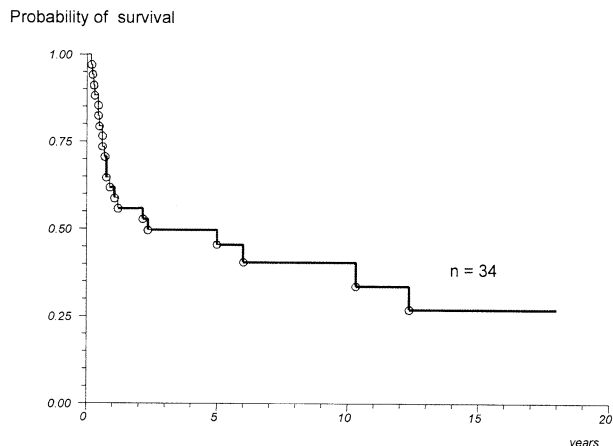


Fig 1. Actuarial survival rate of infants undergoing surgery at ≥ 100 days.

turity, including fluctuating jaundice. At a laparotomy at 168 days she was found to have a membranous type 1 BA and a proximal pin-hole perforation in her bile duct with some localized bile leakage. Liver biopsy and histology of the resected bile duct was indistinguishable from “congenital” BA. The other had a history of fluctuating jaundice and a laparotomy at 119 days, which showed a type 2 BA. There was a mass of inspissated bile around the supraduodenal portion of the common bile duct and a distal perforation. Cirrhosis was confirmed histologically.

Postsurgical Outcome (n = 34)

Twenty-six infants underwent a Kasai portoenterostomy (type 3 [n = 23] and type 1 [n = 3]), and 7 a hepaticojejunostomy (type 1 [n = 4]; type 2 [n = 3]). The infant described above with an acquired type 1 BA had a resection of the atretic segment and duct-to-duct anastomosis. The whole group then was followed up for a median of 2.2 (0.45 to 18) years.

Twelve (34%) children were alive at last follow-up with their native liver (median, 9 [range, 2 to 18] years); 9 (28%) children had undergone liver transplantation (median, 1 [range, 0.18 to 12] years postoperatively), and 13 children have died (median, 0.75 [range, 0.3 to 6] years postoperatively). Eight of the 12 children who are alive with their native liver were anicteric at last follow-up (type III [n = 4], type 1 [n = 2], acquired [n = 2]). Two children have bilirubin levels of 35 and 73 $\mu\text{mol/L}$ at last follow-up, and 1 was alive at 5 years, although the bilirubin level had not been recorded.

Figure 1 illustrates the actuarial survival of those with known outcome (n = 34). The 5- and 10-year survival rates with native liver was 45% and 40%, respectively. Figure 2 shows the survival of infants according to type of BA. There was no real survival advantage for infants with the “correctable” (types 1 and 2, n = 10) versus the

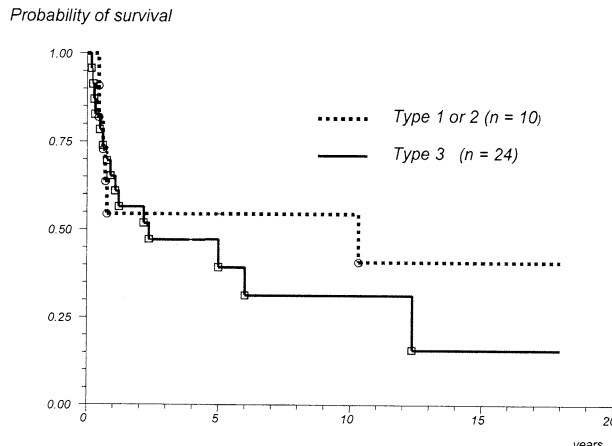


Fig 2. Effect of type of biliary atresia on survival.

“uncorrectable” type 3 BA (n = 24; $P = .42$). Figure 3 shows the survival of infants according to the perception of cirrhosis at the time of operation (n = 12). “Cirrhosis” was based either on a preoperative percutaneous liver biopsy or on macroscopic appearance of the liver at the time of laparotomy. There was no significant survival disadvantage when this feature was diagnosed ($P = .25$).

Ultrasound Review

Twelve of a possible 14 scans, available since January 1986, were reviewed. Of these, 10 were described as showing a homogeneous parenchymal pattern and 2 a finely heterogeneous appearance suggestive of cirrhosis. In the “homogeneous” group, 5 remain jaundice free, and 5 have undergone transplant or have died. Both infants considered “heterogeneous” underwent transplant 2 and 4 months post-Kasai. Thus, the positive predictive value of this observation was 100%, but its negative predictive value was only 50%.

One infant shown at operation to have an acquired

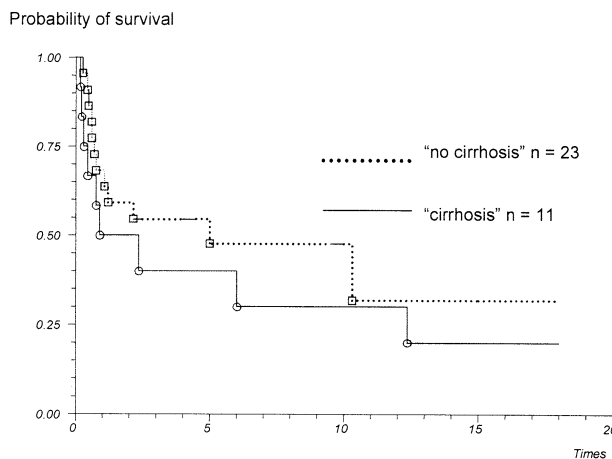


Fig 3. Effect of “cirrhosis” perceived at time of laparotomy.

Table 1. Relationship of Histologic Criteria to Outcome

| Histologic Feature | Alive | Dead/OLT | Significance | PPV | NPV |
|------------------------------------|-------|----------|----------------|------|-----|
| Fibrosis | | | | | |
| 4 | 4 | 7 | | | |
| <4 | 4 | 7 | <i>P</i> = .67 | - | |
| Cholangiolar bile duct destruction | | | | | |
| 3 | 0 | 4 | | | |
| <3 | 8 | 10 | <i>P</i> = .13 | 100% | 56% |
| Parenchymal cholestasis | | | | | |
| 3 | 2 | 3 | | | |
| <3 | 6 | 11 | <i>P</i> = .62 | | |
| Bile duct destruction | | | | | |
| Yes | 5 | 9 | | | |
| No | 3 | 5 | <i>P</i> = .64 | | |
| Giant cell transformation | | | | | |
| Yes | 5 | 6 | | | |
| No | 2 | 9 | <i>P</i> = .18 | 55% | 88% |

type 2 BA showed slight dilatation of the intrahepatic bile ducts, but another with type 1 BA was not discriminated. Two scans suggested intrahepatic parenchymal cystic change, although this was not identified at surgery.

In 11 infants, the median spleen size was 7.5 (range, 4.7 to 9.1) cm, whereas resistance index was 0.79 (range, 0.61 to 0.91). There was no correlation of either variable with age at surgery (*P* = .37, *P* = 0.27, respectively). Similarly, there was no correlation between either variable and outcome.

Histologic Review

Preoperative histologic material was available for review in 22 infants. The degree of fibrosis was assessed as grade 4 (n = 11 [50%]) grade 3 (n = 8 [36%]) and grade 2 (n = 3 [14%]). The degree of cholangiolar bile casts was assessed as grade 3 (n = 4 [18%]) grade 2 (n = 1 [5%]), grade 1 (n = 4 [18%]) and grade 0 (n = 13 [59%]). Lobular (parenchymal) cholestasis was assessed as grade 3 (n = 5 [23%]), grade 2 (n = 2 [55%]), grade 1 (n = 2 [9%]). Two (9%) infants had no evidence of lobular cholestasis. Fourteen (64%) had evidence of bile duct destruction. Giant cells were assessed as grade 3 (n = 3 [14%]), grade 2 (n = 5 [23%]) and grade 1 (n = 3 [14%]). There was no evidence of giant cell transformation in 10 (45%) infants.

Within this histologic review group, 8 underwent successful surgery, whereas 14 either died or underwent transplant. Table 1 shows the results of a χ^2 analysis to determine the relationship of criteria to outcome and shows that no feature was significantly different between the 2 outcomes.

DISCUSSION

The value of the Kasai operation in biliary atresia is now unquestioned, when it is performed by surgeons

experienced in the technique with unrestricted access to the appropriate medical and nutritional support facilities and optimal postoperative care. In the United Kingdom, as a whole, about 55% of infants with BA will be rendered jaundice free¹⁵ having therefore the prospect of short- to medium-term survival with their own liver.

To date, there exists no clinical test that can predict success or failure of the Kasai operation (at whatever age) without actually performing it. However, as the intrinsic liver damage progresses with increasing age, a progressively lower proportion of cases will benefit from a surgical procedure with a minimal chance for success. Previous abdominal surgery is associated with increased risks of postliver transplant complications, including intestinal perforation,²¹ vascular complications, and abdominal infection. The question remains as to when to stop offering an apparently hopeless surgical procedure. Our series, which is the largest from a single center, suggests that even in this subgroup of "elderly" infants, worthwhile restoration of bile flow, loss of jaundice, and even resolution of chronic liver disease can be observed. Overall, about 40% of infants survived to 5 years with their liver—a remarkable statistic.

The conclusions from other studies, which have also sought to answer this specific question above, have varied. In Kasai's own series¹⁶ only 19% of infants operated on from 90 to 120 days, survived to 10 years. Furthermore, there were no long-term survivors in those operated on after 120 days. Chardot et al¹⁷ reported the survival experience of 60 (14%) of 440 infants who underwent a Kasai portoenterostomy aged greater than 90 days in France between 1986 and 1996, and showed that the 5-year survival rate with a native liver was 25% compared with 35% if less than 90 days. Tagge et al¹⁸ reported the experience of 34 infants in the United States and showed that 77% of infants undergoing a Kasai operation at greater than 84 days became anicteric. Finally, Schoen et al¹⁹ reported a small series of 4 infants undergoing Kasai at greater than 90 days, all of which were successful. Toyosaka et al²⁰ reported the oldest successful Kasai operation in a 9-month-old child who had a type 3 BA with cystic change in the common bile duct. Even at that age, cirrhosis was not evident, and the child was rendered anicteric and had been well for 6 years.

It seems likely that some discrepancies in outcome may be, in part, caused by the heterogeneous nature of the older infant with BA. There are those in whom the diagnosis is delayed for nonmedical reasons: failure of the attendants to realize the importance of persisting jaundice and failure of parents to present their children for routine health checks. In these, the intrinsic parenchymal disease is advanced at presentation, and their outlook is, without doubt, poorer. However, there also

seems to be a group who may well have a different type of BA, presumably acquired in the postnatal period, for whom the intrinsic parenchymal disease is not as advanced and after restoration of bile flow would be expected to do well. We have previously used the term *acquired* BA¹⁴ describing 3 infants from our whole series in whom, although technically atretic, it appeared that the process may have been because of a specific cause such as a healed spontaneous perforation or vascular injury. These older infants invariably did well after reconstruction. There also appears to be a higher proportion of the more uncommon types of BA (types 1 and 2) in this group, again suggesting a different etiology and pathology.

Primary transplantation is the alternative for this group of infants, although the literature is small, and specific reports of infants who undergo this option are few.^{10, 21} In the largest, a French multicenter study,¹⁰ 30 infants underwent this option. However, their overall survival rate was significantly worse than infants less than 90 days who underwent a Kasai and later transplantation, if needed, and only similar to infants who underwent Kasai at greater than 90 days and later transplantation. These poor results were principally owing to pretransplant deaths on the waiting list clearly emphasizing that appropriate comparison must begin at the time of listing not simply limiting it to those who actually received a transplant.

Four studies from 3 American centers have attempted to compare the results of primary transplantation versus transplant post-Kasai portoenterostomy.²¹⁻²⁴ In an early report (1988) from Los Angeles, Millis et al²² compared 8 children without portoenterostomy versus 28 who had undergone portoenterostomy. There were no significant differences either in terms of postoperative complications or in the 3-year survival rates. Only those who had undergone repeated attempts at portoenterostomy were disadvantaged. In a later report from the same institution, Goss et al²⁴ analysed the results of transplantation in 190 children, of whom 86% had had portoenterostomy. Previous portoenterostomy was not at all related to patient survival rate in a multivariate analysis of possible variables. Meister et al²³ from San Francisco compared those who had undergone primary transplant, those with previous portoenterostomy, and those with a stoma and portoenterostomy. Only in the latter group was an increased operating time and higher number of reoperations noted. Finally, Sandler et al²¹ compared the results of 57 infants who underwent transplantation for BA, of which 49 had had a previous Kasai operation. Those who received primary transplants, as expected, tended to be younger and smaller. Nevertheless, there was no difference in terms of transfusion requirements, postoperative complications, graft survival, or patient survival, al-

though the operation time tended to be longer in the Kasai group. Interestingly, postoperative bowel perforations were not seen at all in the primary group compared with 22% of those with a previous Kasai. There is some evidence to suggest that there is a reduced incidence of episodes of cellular rejection after liver transplantation during infancy.²⁵ However, surgical difficulties clearly outweigh the potential immunologic benefits of early transplantation. Furthermore, delayed transplantation allows the patient to complete a full course of immunizations and perhaps acquire immunity to some of the community infections.

Intuitively, we felt that if we could identify the infant with "cirrhosis" or the "correctable" types of BA at presentation, then we could perhaps select those for primary transplantation. This proved difficult as judged by our retrospective histologic and ultrasonographic reviews, which we judged to have the best chance of a reproducible assessment. Unfortunately, histologic degree of fibrosis was of no value, and more specific criteria looking at bile duct damage, cholestasis, and giant cells were not discriminatory at all. The use of histologic criteria for the prediction of success or failure in the Kasai procedure (irrespective of the age of the patient) has been controversial. In our own retrospective reviews^{3,29} of BA we have found that no histologic criteria had any bearing on outcome either in terms of clearance of jaundice³ or the later development of portal hypertension and varices.²⁹ Similarly, the large 2-center series from Denver and New York failed to identify liver histology as predictive in a multivariate risk factor analysis.³⁰ Nevertheless, smaller studies such as those by Vasquez-Estevez et al²⁸ and Azarow et al from Toronto³¹ have suggested that features such as syncytial giant cell transformation and lobular inflammation were predictive of poor outcome. The latter study quoted a sensitivity of 86% and specificity of 88% in 31 infants, irrespective of age at Kasai.

Ultrasonographic criteria suggestive of cirrhosis, although specific for a poor outcome, were far from sensitive. Similarly, in terms of identifying the "correctable" types 1 and 2, ultrasound specificity also appeared poor. However, image resolution has improved considerably since the late 1980s, and it is possible that nowadays greater accuracy in defining structural anomalies can be achieved. We also looked at the value of trying to assess the degree of "portal hypertension" or "liver fibrosis" using ultrasonography. Neither spleen size nor calculation of a resistance index seemed to have any predictive value or relationship with age (more than 100 days).

Direct evidence from the literature for stringent selective criteria in this age group is lacking. Chardot et al¹⁷ suggests assessment of nutritional parameters, presence or absence of ascites, and biochemical variables to reflect

synthetic liver function but provides no evidence of their value. A single biochemical marker that enables accurate discrimination between infants with a good or bad prognosis has still to enter clinical practice. Most studies have been compromised because of small numbers or inclusion of postoperative values, although some may prove useful. For instance, Dhawan et al³² recently reported our experience with serum hyaluronic acid (HA) in 84 infants and showed that values of greater than 450 $\mu\text{g/L}$ had a 74% positive predictive value (PPV) and 80% negative predictive value (NPV) for failure. Further, if the analysis was confined to those of 77 days or greater ($n = 23$) then the PPV increases to 85% and the NPV to 50% (ie, it seems to have more value in older age groups).

Some surgeons have used laparoscopy as a diagnostic alternative in BA,³³ and this technique might also separate those that have the appearance of true cirrhosis at presentation without the need for laparotomy. Nevertheless, most reports are of liver biopsy and cholangiography alone rather than a true portal dissection necessary to distinguish between a "correctable" type 2 and "uncorrectable" type 3 BA.

Does it matter if a Kasai operation is done in infants with advanced liver disease? As previous studies have suggested, in terms of the later transplant operation, there is no real difference in morbidity or mortality rates

between those that have a primary or a secondary transplant (specifically without stoma or revisions). Nevertheless, older infants do have increased morbidity and perhaps mortality rate compared with the younger ones undergoing portoenterostomy and particularly problematic are those with clinical ascites. We have noted difficulties with the management of ascites postlaparotomy occasionally leading to wound breakdown or prolonged fluid losses through drain sites. In the French national study,¹⁷ about 5% of deaths in their greater-than 90 days group were attributable to post-Kasai complications such as rapid decompensation of advanced liver disease, although it remains uncertain as to what role the surgery itself played. Thus, perhaps paradoxically, especial surgical care must be taken with their operation and postoperative management to minimize avoidable complications.

It remains our view that unless exceptional criteria can be met, there is clear value in performing a Kasai portoenterostomy in those infants widely considered as "old" at presentation. Although perhaps only 30% to 40% will be rendered anicteric and have a good quality of life, the alternative of unselected primary transplantation denies those the opportunity of life without immunosuppression and would cause unnecessary strain to an already stressed organ donor system.

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