Management of biliary atresia: To transplant or not to transplant

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Abstract
Kasai procedure (KP) and liver transplantation (LT) represent the only therapeutic options for patients with biliary atresia (BA), the most common indication for LT in the pediatric population. However, KP represents by no means a radical option but rather a bridging one, as nearly all patients will finally require a liver graft. More and more experts in the field of transplant surgery propose that maybe it is time for a paradigm change in BA treatment and abandon KP as transplantation seems inevitable. Inadequacy of organs yet makes this option currently not feasible, so it seems useful to find ways to maximize the efficacy of KP. In previous decades, multiple studies tried to identify these factors which opt for better results, but in general, outcomes of KP have not improved to the level that was anticipated. This review provides the framework of conditions which favor native liver survival after KP and the ones which optimize a positive LT outcome. Strategies of transition of care at the right time are also presented, as transplantation plays a key role in the surgical treatment of BA. Future studies and further organization in the transplant field will allow for greater organ availability and better outcomes to be achieved for BA patients.

Key Words: Biliary atresia; Kasai procedure; Portoenterostomy; Native liver survival; Liver transplantation

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Core Tip: Timely diagnosis of biliary atresia (BA) is critical to optimizing the outcomes of Kasai procedure (KP), which should be performed as early as possible. Children with a delayed diagnosis of BA at high risk of early KP failure or those presenting with clear evidence of decompensated cirrhosis should be considered for primary liver transplantation (LT). Early KP failure requiring salvage LT within the first 2-3 years of life occurs in nearly half of all children with BA but even those with a successful KP need life-long monitoring for progression of liver disease that may require salvage LT.

INTRODUCTION

Biliary atresia (BA) represents the most common indication for pediatric liver transplantation (LT) worldwide, accounting for half of LTs in children and one-tenth of all LTs[1]. Kasai was the first who performed successful drainage of the bile into the intestine after resecting the obliterated extrahepatic portion of the biliary tree[2]. Although the Kasai procedure (KP) is considered to be the first-line treatment, the progressive liver injury seen in most patients with BA results in 5-year post-procedural native liver survival (NLS) between 38%-40% even at experienced centers[3-5]. As a result, most patients will need a salvage LT (sLT) at some point during their lifetime. The overall low lifetime NLS creates an important dilemma for pediatric LT experts: Should LT be considered primary therapy in infants with BA and a high likelihood of KP failure, or should it be utilized as a salvage therapy? This review aims to highlight the key concepts around this question and to provide an update regarding the management and outcomes of KP and LT for BA.

PATHOPHYSIOLOGY

The pathogenesis of BA is not fully understood but appears to be multifactorial. Approximately 15% of patients with BA have associated congenital malformations, such as abdominal and thoracic heterotaxia, polysplenia, asplenia, and intestinal malrotation[6]. Viruses, such as cytomegalovirus, herpes virus, Epstein-Barr virus, and reovirus, may also contribute to a certain extent in the pathogenesis of BA. Additional factors which may contribute are neonatal immune dysregulation and environmental toxins[7,8]. While radiologic studies, such as hepatobiliary iminodiacetic acid scan, may suggest the diagnosis, failure to visualize the biliary tree during intra-operative cholangiography remains the gold standard for diagnosing BA. Characteristic findings on liver biopsy include edematous fibroplasia with bile ductular proliferation and bile plugs[9].

FACTORS ASSOCIATED WITH NATIVE LIVER SURVIVAL AFTER KASAI

Before the Kasai’s report[2], BA was a fatal disease. Unfortunately, KP does not prevent progressive hepatic injury, which gradually leads to cirrhosis and end-stage liver disease (ESLD) in most patients. Numerous studies have attempted to identify the factors predictive of NLS, however, the majority are from single centers and retrospective in nature[1,3,10-15]. Additionally, many of them are limited to univariate analysis, and thus careful interpretation of these results is warranted (Table 1).

The main histologic characteristics of BA are increased cholestasis, marked fibrosis, and ductular proliferation, while the mechanisms behind fibrinogenesis are still under investigation. There seemed to be a clear association between the degree of preoperative fibrosis in the liver biopsy and poor NLS[10,16-18]. Another important histologic finding is intrahepatic duct size, as ducts less than 200 μm represent a risk factor for NLS[19]. However, a large prospective study from 16 centers in North...
Table 1 Factors reported to be associated with native liver survival

| Before the Kasai procedure | After the Kasai procedure | Other |
|----------------------------|---------------------------|-------|
| Liver fibrosis              | Jaundice clearance        | Specialized institution |
| Ductal size                 | Cholangitis               |       |
| Biliary atresia type according to Ohi classification | Total bilirubin |       |
| Portal hypertension         | Serum creatinine          |       |
| Biliary atresia splenic malformation syndrome | Portal hypertension |       |
| Age at the time of Kasai procedure | Serum albumin |       |
|                            | Corticosteroids           |       |
|                            | Antibiotics               |       |

America found no association between liver fibrosis severity, measured histologically by the 6 grade Ishak score, and NLS. Instead, gross appearance of the liver at the time of surgery was predictive of poor NLS[20]. Regarding BA types based on the Ohi classification, patients with Ohi type 2 and 3 BA appear to have worse outcomes than Ohi type 1[20].

Duché et al[21] showed that elevated portal pressure, polysplenia syndrome, and complete atresia of the extrahepatic biliary remnant were independently associated with worse NLS , as there were lower chances of successful postoperative jaundice clearance. The latter is considered extremely important for a proper KP[22,23]. Superina et al[20] have also shown the effect of early jaundice clearance on improved NLS. Similar to Duché et al[21], Superina et al[20] reported the hazardous effect of BA splenic malformation syndrome (BASM) on NLS, which surprisingly was not associated with jaundice clearance after KP. The presence of splenic anomalies as an indicator of poor prognosis has also been documented in other studies[3,24]. The embryological aspects of this malformation have been studied by Davenport et al[25] and Karrer et al[26], yet the pathogenesis is still unclear. Notably, a study from Sendai, Japan reported similar survival between patients with isolated BA vs BA plus BASM and no associated cardiac defects[27]. Sasaki et al[28] demonstrated that presence of symptomatic portal hypertension (gastro-esophageal varices requiring treatment), but not hypersplenism nor cholangitis, was found to be a significant risk factor in multivariate logistic regression analysis for NLS.

Age at the time of KP plays a vital role in NLS[5]. There is a general consensus among pediatric surgeons that the sooner the diagnosis and KP is performed, the better the outcome. Several cutoffs between 7-10 wk after birth have been proposed in the literature[3,10,20,29]. It is noteworthy that the age at KP in the United States has not decreased significantly over time[30].

Expertise in KP offered in high-volume centers and centralization of care for patients with BA has been thought of playing a key role in improving outcomes. Although excellent results can be obtained even in centers with relatively little experience[31], this theory seems to have a strong basis[3]. The so-called “center effect” reflects the experience of the teams at individual centers, and in certain countries in Europe (e.g., United Kingdom, Finland) centralization of care to supraregional centers has been effective in optimizing outcomes nationwide[32,33].

Regarding postoperative factors, recurrent cholangitis episodes have been associated with KP failure in multiple studies[18,34-36]. More specifically, Wildhaber et al[18] demonstrated an approximately double risk for patients with bridging fibrosis and postoperative cholangitis compared to those with cholangitis alone, showing the impact of this underlying condition. Moreover, Wu et al[35] noted that patients with BA and inadequate bile drainage had more cholangitis episodes than those with adequate bile drainage, while the occurrence of cholangitis was associated with decreased NLS in both groups of patients. In contrast, a single-center study from California showed no association between cholangitis episodes and the need for LT[19], and the same was reported in a more recent study from Japan[28]. It is well-established that BA is an obstructive intra- and extrahepatic cholangiopathy, while KP can only solve the extrapancreatic part of the problem. Therefore, for optimal outcomes, KP can be combined with regimes dealing with intrahepatic obstruction, inflammation, and bile infection[37]. Specifically, ursodeoxycholic acid has been utilized often for this purpose due to its immunomodulatory and cytoprotective effects[38].
Jain et al.\textsuperscript{39} described several parameters associated with an increased risk for requiring LT after 16 years of age. They reported that among BA patients achieving NLS until the age of 16 years, only serum total bilirubin and creatinine were associated with higher risk of requiring LT. A retrospective study from Australia and Canada showed that a serum albumin level below 35 g/L was a poor prognostic indicator in infants with BA who were no longer jaundiced at 3 mo after KP\textsuperscript{40}.

Corticosteroids are well-known modulators of BA inflammation as they reduce the production of inflammatory cytokines (tumor necrosis factor-\(\alpha\), interleukin-1, interleukin-8), prostaglandins, and nitric oxide\textsuperscript{41}. They also seem to have other choleric effects, which have not been studied as extensively. Results from early studies on the use of corticosteroids showed a benefit in survival in BA patients\textsuperscript{42-45}. A randomized controlled trial from 2007 showed that corticosteroids had a benefit on the rate of reduction of bilirubin early postoperatively, yet they did not reduce the need for LT\textsuperscript{46}. The more recent START randomized clinical trial compared 70 children receiving intravenous methylprednisolone (4 mg/kg/d for 2 wk) and oral prednisolone (2 mg/kg/d for 2 wk) followed by a tapering protocol for 9 wk with 70 children receiving placebo initiated within 3 d of KP\textsuperscript{47}. The study showed that high-dose steroids after KP did not significantly improve bile drainage at 6 mo, although a small clinical benefit could not be excluded\textsuperscript{47}. However, treatment with steroids was associated with earlier onset of serious adverse events\textsuperscript{47}. A meta-analysis published in 2015 showed no significant difference in jaundice clearance for patients who received steroids overall; nonetheless, sensitivity analysis excluding studies on the use of high- or low-dose steroids and including only studies on the use of moderate-high dose steroids (prednisolone 4-5 mg/kg/d) showed a higher jaundice clearance rate at 6 mo post-KP\textsuperscript{48}. Prednisolone is the most frequently prescribed steroid in most studies, but dexamethasone and hydrocortisone have also been described in the literature\textsuperscript{49}. The possible side effects of long-term steroid use should not be neglected.

There is limited knowledge about potential benefit of post-KP use of antibiotics. The commonest intravenous regimen in a survey of European practice is a combination of piperacillin-tazobactam and gentamicin\textsuperscript{50}. A randomized clinical trial by Bu et al\textsuperscript{51} demonstrated a positive impact of post-KP use of trimethoprim–sulfamethoxazole or oral neomycin, while a recent systematic review of four articles by Dechaurun et al\textsuperscript{52} presented ambiguous results with three studies suggesting the presence of a potential benefit in using antibiotics. The need for high-quality evidence in the form of prospective studies in this field is evident.

\textbf{LT OUTCOMES}

The majority of patients with BA will progress to ESLD requiring evaluation for LT at some point in their life. Since Kasai’s first description\textsuperscript{2}, there have not been significant changes to the technique of KP, and long-term NLS has not significantly improved. Unfortunately, even patients who manage to survive more than 20 years after KP have histological, clinical, or ultrasonographic evidence of significant chronic liver disease\textsuperscript{53,54}. Portal hypertension is also commonly observed in BA patients at some point after KP\textsuperscript{53,54}.

sLT is considered when patients who had undergone KP develop ESLD. A retrospective study from the United States reported a higher incidence of cholangitis, sepsis, and bacteremia in the baseline characteristics of patients who underwent sLT, compared with those who underwent only KP\textsuperscript{55}. The authors also compared the outcomes between primary liver transplantation (pLT) and KP, regardless of whether patients eventually required sLT. Early survival was higher in the KP group, but long-term survival was significantly better in pLT group (5-year survival 88% for KP vs 94% for pLT)\textsuperscript{55}. sLT was also associated with an increased risk of death compared to pLT, which may be attributed to the technical difficulties of sLT in the setting of previous KP and hilar dissection. Recipients of sLT for BA have been reported to have a higher incidence of infectious and vascular complications and intestinal perforation compared to pLT recipients, likely due to previous surgical interventions\textsuperscript{56-58}. The incidence of pLT for BA varies from 10%-11% in Canada, Switzerland, and Germany to 3%-4% in the Netherlands, United Kingdom, and France and to 0.1% in Japan\textsuperscript{59}, so the decision regarding the management of BA may vary among different healthcare systems.

Nevertheless, there are studies reporting equivalent LT outcomes between patients with and without a previous KP. The findings of equivalent post-LT survival
regardless of prior KP support the recommendation for a staged approach for the treatment of BA, starting with KP and progressing to LT only when necessary[60-63]. It is argued that in this way, KP delays the need for LT and allows not only for the improvement of the child’s nutritional status but also for their size to increase and to increase the potential size-matched organ donor pool. A multicenter study from 39 centers in the USA and Canada failed to demonstrate an effect of prior KP on LT outcome[64]. Cowles et al[65] reported on 71 children who underwent LT for BA, 61 of whom had previously undergone KP, and they observed no clear difference in the outcomes between the two groups. A 2016 meta-analysis reported no difference in 1- and 5-year patient and graft survival between patients who underwent KP and those who did not, yet patients who had undergone KP prior to LT had an increased risk of postoperative infection[66].

Another interesting aspect is the comparison of post-transplant after KP outcomes between children and adults. Kyoden et al[67] found no significant differences in survival with a 5-year patient survival of 90% in both age groups, yet a large retrospective study from Japan demonstrated a clear survival benefit in the pediatric population (5-year patient survival 86.7% in children vs 69.7% in adults)[68]. In both studies the patients received a living donor graft[67,68]. A more recent single-center study from King’s College Hospital also showed superior patient survival after deceased donor LT for BA patients listed as children (n = 22) compared to those listed as adults (n = 14), yet the results did not reach statistical significance because of the limited study sample[69].

The type of liver graft may also be a major prognostic factor. Living donation has expanded the donor pool and also provided recipients with organs which appear to be of better quality than the deceased ones[70]. Multiple studies agree that living donor grafts have superior outcomes in patients with BA[60], but there are also reports challenging this theory[61,63,64]. A study from 1996 had suggested that LT using reduced-size grafts (only part of the donor liver is used for the graft, and the remaining resected liver is discarded) may not be the best option for BA due to inferior outcomes[62]. However, since reduced-size grafts were mostly utilized in emergency situations, the authors stated that after censoring these, they found no significant difference in patient survival between elective reduced-size and whole liver grafts[62]. A more recent study using national registry data showed that the effect of donor allograft is related to recipient weight for children with BA[71]. Specifically, for children ≤ 7 kg, reduced size grafts and living donor grafts had decreased risk of graft failure compared to whole grafts, for children 7-14 kg living donor grafts had decreased risk of graft failure compared to both reduced size and whole grafts, while for children > 14 kg there was no difference in graft failure by allograft type[71].

There are several studies that tried to identify predictors of a successful LT in children with BA (Table 2). Fouquet et al[61] demonstrated that BASM, intraoperative complications (hemorrhage, intestinal injury, vascular thrombosis), and hospitalization in the intensive care unit were associated with an increased risk of death. Utterson et al[64] reported that infant recipient (≤ 11 mo), use of cyclosporine vs tacrolimus, growth deficit, and re-transplantation were associated with post-LT mortality. Living donation, technological refinements, increased surgical experience, and advances in anesthesia and in immunosuppression will play a key role in improving post-LT outcomes.

TRANSITION OF CARE

So, the main question remains: To transplant or not to transplant? For many decades it was considered that KP must be the first choice for patients with BA, serving as a bridging therapy to delay or even avoid the need for LT. Today it is well-established that most BA patients will eventually require LT at some point in their lifetime, yet the demand for donor livers continuously exceeds the supply. LT has matured to the stage where in most centers excellent long-term survival can be achieved despite the technical challenges of sLT following KP. However, the excellent long-term outcomes of pLT suggest this is also a reasonable alternative treatment option for certain patients[59]. pLT is now being more frequently considered for children with BA at a very high likelihood of early failure of KP, challenging the traditional treatment paradigm.

For children who have undergone KP, the best next step is to ensure adequate follow-up and appropriate transition of care from childhood to adulthood so as to continuously monitor for manifestations of ESLD and refer for LT when needed. Progressive jaundice, recurrent bacterial cholangitis, portopulmonary hypertension,
Table 2 Factors associated with liver transplant outcomes

| Patient characteristics                  | Surgical characteristics                  |
|-----------------------------------------|------------------------------------------|
| Age at the time of liver transplant     | Previous Kasai procedure                 |
| Biliary atresia splenic malformation    | Intraoperative complications (hemorrhage, intestinal injury, vascular thrombosis) |
| Growth deficit                          | Allograft type                            |
| Hospitalization in the intensive care unit | Re-transplantation                      |
| Type of immunosuppression               |                                          |

and hepatopulmonary syndrome warrant evaluation for LT. Implementation of objective scoring systems, including Model for End-stage Liver Disease and Pediatric End-stage Liver Disease score systems, have decreased the pediatric waitlist mortality and increased the number of patients receiving a deceased donor liver graft[55]. However, several manifestations of ESLD are not adequately reflected in these scoring systems, and thus many children with BA eventually require exception points to undergo LT[72]. Mortality risk has been shifted gradually to the pre-transplant period, and peri-transplant risks are mainly related to patient’s condition[73]. Receiving an LT at a young age allows for greater use of left lateral segment graft from a living donor without affecting the deceased donor pool. From another point of view, KP is far more cost-effective compared to pLT[74].

Timely diagnosis of BA is critical to optimizing the outcomes of KP, which should be performed as early as possible. Children with a delayed diagnosis of BA at high risk of early KP failure or those presenting with clear evidence of decompensated cirrhosis should be considered for pLT. Early KP failure requiring sLT within the first 2-3 years of life occurs in nearly half of all children with BA, but even those with a successful KP need life-long monitoring for progression of liver disease that may require sLT.

CONCLUSION

In conclusion, cooperation between pediatric and adult hepatologists, pediatric surgeons, and transplant surgeons is necessary for the management of BA patients. Close and long-term follow-up is required to monitor for manifestations of ESLD that may warrant evaluation for LT, as well as to improve quality of life along with survival outcomes. More prospective multicenter studies are needed to demonstrate a clear conclusion about the proper management of BA.

REFERENCES

1 Sokol RJ, Shepherd RW, Superina R, Bezerra JA, Robuck P, Hoofnagle JH. Screening and outcomes in biliary atresia: summary of a National Institutes of Health workshop. Hepatology 2007; 46: 566-581 [PMID: 17661405 DOI: 10.1002/hep.21790]

2 Kasai M. A new operation for “non-correctable” biliary atresia: hepatic portoenterostomy. Shujutsu 1959; 13: 733-739

3 Chardot C, Buet C, Serinet MO, Golmard JL, Lachaux A, Roquelaure B, Gottrand F, Brouté P, Dabadie A, Gauthier F, Jacquemin E. Improving outcomes of biliary atresia: French national series 1986-2009. J Hepatol 2013; 58: 1209-1217 [PMID: 23402746 DOI: 10.1016/j.jhep.2013.01.040]

4 Bondoc AJ, Taylor JA, Alonso MH, Nathan JD, Wang Y, Balistreri WF, Bezerra JA, Ryckman FC, Tiao GM. The beneficial impact of revision of Kasai portoenterostomy for biliary atresia: an institutional study. Ann Surg 2012; 255: 570-576 [PMID: 22258066 DOI: 10.1097/SLA.0b013e318243a36c]

5 Serinet MO, Wildhaber BE, Brouté P, Lachaux A, Sarles J, Jacquemin E, Gauthier F, Chardot C. Impact of age at Kasai operation on its results in late childhood and adolescence: a rational basis for biliary atresia screening. Pediatrics 2009; 123: 1280-1286 [PMID: 19403492 DOI: 10.1542/peds.2008-1949]

6 Khalil BA, Perera MT, Mirza DF. Clinical practice: management of biliary atresia. Eur J Pediatr 2010; 169: 395-402 [PMID: 20020156 DOI: 10.1007/s00431-009-1125-7]

7 Harper P, Plant JW, Unger DB. Congenital biliary atresia and jaundice in lambs and calves. Aust Vet J 1990; 67: 18-22 [PMID: 2334368 DOI: 10.1111/j.1751-0813.1990.tb07358.x]

8 Mack CL, Sokol RJ. Unraveling the pathogenesis and etiology of biliary atresia. Pediatr Res 2005; 57: 87R-94R [PMID: 15817506 DOI: 10.1203/1.PDR.0000159567.57354.47]
Vij M, Rela M. Biliary atresia: pathology, etiology and pathogenesis. Future Sci OA 2020; 6: FSO466 [PMID: 32518681 DOI: 10.2144/fsoa-2019-0153]

Altman RP, Lilly JR, Greenfield J, Weinberg A, van Leeuwen K, Flanagan L. A multivariable risk factor analysis of the portoenterostomy (Kasai) procedure for biliary atresia: twenty-five years of experience from two centers. Ann Surg 1997; 226: 348-353; discussion 353-355 [PMID: 9339941 DOI: 10.1097/00000658-199709000-00014]

Davenport M, Kerker N, Mieli-Vergani G, Mowat AP, Howard ER. Biliary atresia: the King's College Hospital experience (1974-1995). J Pediatr Surg 1997; 32: 479-485 [PMID: 9094023 DOI: 10.1016/0022-3468(97)90611-4]

Pietrobatista A, Mosca A, Liccardo D, Alterio T, Grimaldi C, Basso M, Saffiotti MC, Corte CD, Spada M, Candusso M. Does the Treatment After Kasai Procedure Influence Biliary Atresia Outcome and Native Liver Survival? J Pediatr Gastroenterol Nutr 2020; 71: 446-451 [PMID: 32960536 DOI: 10.1097/MPG.0000000000002837]

Wang Z, Chen Y, Peng C, Pang W, Zhang T, Wu D, Shen Q, Li M. Five-year native liver survival analysis in biliary atresia from a single large Chinese center: The death/liver transplantation hazard change and the importance of rapid early clearance of jaundice. J Pediatr Surg 2019; 54: 1680-1685 [PMID: 30518490 DOI: 10.1016/j.jpedsurg.2018.09.025]

Huang CY, Chang MH, Chen HL, Ni YH, Hsu HY, Wu YF. Bilirubin level 1 week after hepatopancreatoenterostomy predicts native liver survival in biliary atresia. Pediatr Res 2020; 87: 730-734 [PMID: 31618755 DOI: 10.1007/s12633-019-0610-6]

Ramos-Gonzalez G, Elisofon S, Dee EC, Staffa SJ, Medford S, Lillehei C, Kinn HB. Predictors of Need for Liver Transplantation in Children Undergoing Hepatopancreatoenterostomy for Biliary Atresia. J Pediatr Surg 2019; 54: 1127-1131 [PMID: 30857951 DOI: 10.1016/j.jpedsurg.2019.02.051]

Schweizer P, Schweizer M, Schelling K, Kirschner HJ, Schittenhelm C. Prognostic of extrahepatic bile-duct atresia after hepatopancreatoenterostomy. Pediatr Surg Int 2000; 16: 351-355 [PMID: 10955561 DOI: 10.1007/s003830000385]

Weerasingoriya VS, White FV, Shepherd RW. Hepatic fibrosis and survival in biliary atresia. J Pediatr 2004; 144: 123-125 [PMID: 14722530 DOI: 10.1016/j.jpeds.2003.09.042]

Wildhaber BE, Coran AG, Drongowski RA, Hirschl RB, Geiger JD, Lelli JL, Teitelbaum DH. The Kasai portoenterostomy for biliary atresia: A review of a 27-year experience with 81 patients. J Pediatr Surg 2003; 38: 1480-1485 [PMID: 14577071 DOI: 10.1016/s0022-3468(03)00499-8]

Baer J, Zuppau C, Klooster M. Biliary atresia—a fifteen-year review of clinical and pathologic factors associated with liver transplantation. J Pediatr Surg 2004; 39: 800-803 [PMID: 15185199 DOI: 10.1016/j.jpedsurg.2004.02.020]

Superina R, Magee JC, Brandt ML, Healey PJ, Tiao G, Ryckman F, Karrer FM, Iyer K, Fecteau A, West K, Burns RC, Flake A, Lee H, Lowell JA, Dillon P, Colombani P, Ricketts R, Li Y, Moore J, Wang KS; Childhood Liver Disease Research and Education Network. The anatomic pattern of biliary atresia identified at time of Kasai hepatopancreatoenterostomy and early postoperative clearance of jaundice are significant predictors of transplant-free survival. Ann Surg 2011; 254: 577-585 [PMID: 21886974 DOI: 10.1097/SLA.S0000000000000095]

Duché M, Fabre M, Kretzschmar B, Serinet F, Gauthier F, Chardot C. Prognostic value of portal pressure at the time of Kasai operation in patients with biliary atresia. J Pediatr Gastroenterol Nutr 2006; 43: 640-645 [PMID: 17130742 DOI: 10.1097/01.mp.0000235754.14488.9]

Karrer FM, Price MR, Bensard DD, Sokol RJ, Narkewicz MR, Smith DJ, Lilly JR. Long-term results with the Kasai operation for biliary atresia. Arch Surg 1996; 131: 493-496 [PMID: 8624194 DOI: 10.1001archs.1996.01430170039006]

McKierman PJ, Baker AJ, Lloyd C, Mieli-Vergani G, Kelly DA. British paediatric surveillance unit study of biliary atresia: outcome at 13 years. J Pediatr Gastroenterol Nutr 2004; 48: 78-81 [PMID: 19172128 DOI: 10.1097/MP.0b013e31817dd0de]

Vazquez J, López Gutierrez JC, Gámez M, López-Santamaría M, Murcia J, Larrauri J, Díaz MC, Jara P, Tovar JA. Biliary atresia and the polysplenia syndrome: its impact on final outcome. J Pediatr Surg 1995; 30: 485-487 [PMID: 7760248 DOI: 10.1016/0022-3468(95)90062-4]

Davenport M, Savage M, Mowat AP, Howard ER. Biliary atresia splenic malformation syndrome: an etiologic and prognostic subgroup. Surgery 1993; 113: 662-668 [PMID: 8506525]

Karrer FM, Hall RJ, Lilly JR. Biliary atresia and the polysplenia syndrome. J Pediatr Surg 1991; 26: 524-527 [PMID: 2068100 DOI: 10.1016/0022-3468(91)90967-r]

Nio M, Wada M, Sasaki H, Tanaka H, Watanabe T. Long-term outcomes of biliary atresia with splenic malformation. J Pediatr Surg 2015; 50: 2124-2127 [PMID: 26613366 DOI: 10.1016/j.jpedsurg.2015.08.040]

Sasaki H, Tanaka H, Wada M, Kazama T, Nakamura M, Kudo H, Okubo R, Sakurai T, Nio M. Analysis of the prognostic factors of long-term native liver survival in survivors of biliary atresia. Pediatr Surg Int 2016; 32: 839-843 [PMID: 27464487 DOI: 10.1007/s00383-016-3934-x]

Lang T, Kappler M, Dietz H, Harms HK, Berete-Harms R. Biliary atresia: which factors predict the success of a Kasai operation? Eur J Med Res 2000; 5: 110-114 [PMID: 10756164]

Raval MV, Dzakovic A, Bentrem DJ, Reynolds M, Superina R. Trends in age for hepatopancreatoenterostomy in the United States. Surgery 2010; 148: 785-791; discussion 791-792 [PMID: 20769342 DOI: 10.1016/j.surg.2010.07.028]

Shneider BL, Brown MB, Haber B, Whittington PF, Schwarz K, Squires R, Bezerra J, Shepherd B, Rosenthal P, Hoofnagle JH, Sokol RJ; Biliary Atresia Research Consortium. A multicenter study of...
the outcome of biliary atresia in the United States, 1997 to 2000. J Pediatr 2006; 148: 467-474 [PMID: 16674706 DOI: 10.1016/j.jpeds.2005.12.054]

32 Davenport M, Ong E, Sharif K, Alizai N, McLean P, Hadzic N, Kelly DA. Biliary atresia in England and Wales: results of centralization and new benchmark. J Pediatr Surg 2011; 46: 1689-1694 [PMID: 21929755 DOI: 10.1016/j.jpedsurg.2011.04.013]

33 Lampela H, Ritvanen A, Kosola S, Koivusalo A, Rintala R, Jalanko H, Pakarinen M. National centralization of biliary atresia care to an assigned multidisciplinary team provides high-quality outcomes. Scand J Gastroenterol 2012; 47: 99-107 [PMID: 22171974 DOI: 10.3109/00365521.2011.627446]

34 Lünsmann K, Schweizer P. The influence of cholangitis on the prognosis of extrahepatic biliary atresia. Eur J Pediatr Surg 1999; 9: 19-23 [PMID: 10207698 DOI: 10.1055/s-2008-1072206]

35 Wu ET, Chen HL, Ni YH, Lee PI, Hsu HY, Lai HS, Chang MH. Bacterial cholangitis in patients with biliary atresia: impact on short-term outcome. Pediatr Surg Int 2001; 17: 390-395 [PMID: 11527173 DOI: 10.1007/s003830005753]

36 Koga H, Wada M, Nakamura H, Miyano G, Okawada M, Lane GJ, Okazaki T, Yamataka A. Factors influencing jaundice-free survival with the native liver in post-portoenterostomy biliary atresia patients: results from a single institution. J Pediatr Surg 2013; 48: 2368-2372 [PMID: 24314172 DOI: 10.1016/j.jpedsurg.2013.08.007]

37 Sokol RJ, Mack CL. Optimizing outcomes and bridging biliary atresia into adulthood. Hepatology 2005; 41: 231-233 [PMID: 15657917 DOI: 10.1002/hep.20575]

38 Balisterri WF. Bile acid therapy in pediatric hepatobiliary disease: the role of ursodeoxycholic acid. J Pediatr Gastroenterol Nutr 1997; 24: 573-589 [PMID: 9161955 DOI: 10.1097/00005176-199705000-00016]

39 Jain V, Burford C, Alexander EC, Sutton H, Dhawan A, Joshi D, Davenport M, Heaton N, Hadzic N, Samyn M. Prognostic markers at adolescence in patients requiring liver transplantation for biliary atresia in adulthood. J Hepatol 2019; 71: 71-77 [PMID: 30876944 DOI: 10.1016/j.jhep.2019.03.005]

40 Nightingale S, Stormon MO, O’Loughlin EV, Shun A, Thomas G, Benchimol EI, Day AS, Adams S, Shi E, Ooi CY, Kamath BM, Fecteau A, Langer JC, Roberts EA, Ling SC, Ng VL. Early Posthepatopancreatectomy Predictors of Native Liver Survival in Biliary Atresia. J Pediatr Gastroenterol Nutr 2017; 64: 203-209 [PMID: 28107282 DOI: 10.1097/MPG.0000000000001289]

41 Mack CL, Tucker RM, Sokol RJ, Karrer FM, Kotzin BL, Whittington PF, Miller SD. Biliary atresia is associated with CD4+ Th1 cell-mediated portal tract inflammation. Pediatr Res 2004; 56: 79-87 [PMID: 15128911 DOI: 10.1203/01.PDR.0000130480.51066.FB]

42 Karrer FM, Lilly JR. Corticosteroid therapy in biliary atresia. J Pediatr Surg 1985; 20: 693-695 [PMID: 4087100 DOI: 10.1016/0022-3468(85)80026-9]

43 Muraji T, Higashimoto Y. The improved outlook for biliary atresia with corticosteroid therapy. J Pediatr Surg 1997; 32: 1103-1106; discussion 1106-1107 [PMID: 9247243 DOI: 10.1016/0022-3468(97)90408-5]

44 Dillon PW, Owings E, Cilley R, Field D, Cumow A, Georgeson K. Immunosuppression as adjuvant therapy for biliary atresia. J Pediatr Surg 2001; 36: 80-85 [PMID: 11150442 DOI: 10.1053/jpsu.2001.20013]

45 Meyers RL. Book LS, O’Gorman MA, Jackson WD, Black RE, Johnson DG, Matlak ME. High-dose steroids, ursodeoxycholic acid, and chronic intravenous antibiotics improve bile flow after Kasai procedure in infants with biliary atresia. J Pediatr Surg 2003; 38: 406-411 [PMID: 12632357 DOI: 10.1053/jpsu.2003.50069]

46 Davenport M, Stringer MD, Tizzard SA, McLean P, Mieli-Vergani G, Hadzic N. Randomized, double-blind, placebo-controlled trial of corticosteroids after Kasai portoenterostomy for biliary atresia. Hepatology 2007; 46: 1821-1827 [PMID: 17935230 DOI: 10.1002/hep.21873]

47 Bezerra JA, Spino C, Magee JC, Shneider BL, Rosenthal P, Wang KS, Erlichman J, Haber B, Hertel PM, Karpen SJ, Kerkar N, Loomes KM, Mollepton JP, Murray KF, Romero R, Schwarz KB, Shepherd R, Suchy FJ, Turmelle YP, Whittington PF, Moore J, Sherker AH, Robuck PR, Sokol RJ; Childhood Liver Disease Research and Education Network (ChLDREN). Use of corticosteroids after hepatoportoenterostomy for bile drainage in infants with biliary atresia: the START randomized controlled trial. JAMA 2014; 311: 1750-1759 [PMID: 24794368 DOI: 10.1001/jama.2014.2623]

48 Chen Y, Nah SA, Chiang L, Krishnaswamy G, Low Y. Postoperative steroid therapy for biliary atresia: Systematic review and meta-analysis. J Pediatr Surg 2015; 50: 1590-1594 [PMID: 26143225 DOI: 10.1016/j.jpedsurg.2015.05.016]

49 Zhang D, Yang HY, Jia J, Zhao G, Yue M, Wang JX. Postoperative steroids after Kasai portoenterostomy for biliary atresia: a meta-analysis. Int J Surg 2014; 12: 1203-1209 [PMID: 25224699 DOI: 10.1016/j.jsur.2014.08.407]

50 Wong ZH, Davenport M. What Happens after Kasai for Biliary Atresia? Eur J Pediatr Surg 2019; 29: 1-6 [PMID: 30130826 DOI: 10.1055/s-0038-1668146]

51 Bu LN, Chen HL, Chang CJ, Ni YH, Hsu HY, Lai HS, Hsu WM, Chang MH. Prophylactic oral antibiotics in prevention of recurrent cholangitis after the Kasai portoenterostomy. J Pediatr Surg 2003; 38: 590-593 [PMID: 12677572 DOI: 10.1053/jpsu.2003.50128]

52 Decharun K, Leys CM, West KW, Finnell SM. Prophylactic Antibiotics for Prevention of Cholangitis in Patients With Biliary Atresia Status Post-Kasai Portoenterostomy: A Systematic Review. Clin Pediatr (Phila) 2016; 55: 66-72 [PMID: 26183324 DOI: 10.1177/0009922815594760]

53 Lykavieris P, Chardot C, Sokhn M, Gauthier F, Valayer J, Bernard O. Outcome in adulthood of...
biliary atresia: a study of 63 patients who survived for over 20 years with their native liver. *Hepatology* 2005; 41: 366-371 [PMID: 15660386 DOI: 10.1002/hep.20547]

54 de Vries W, Homan-Van der Veen J, Hulscher JB, Hoekstra-Weebers JE, Houwen RH, Verkade HJ; Netherlands Study Group of Biliary Atresia Registry. Twenty-year transplant-free survival rate among patients with biliary atresia. *Clin Gastroenterol Hepatol* 2011; 9: 1086-1091 [PMID: 21820397 DOI: 10.1016/j.cgh.2011.07.024]

55 Lee Van E, Matsuoka L, Cao S, Groschen S, Alexopoulos S. Biliary-Enteric Drainage vs Primary Liver Transplant as Initial Treatment for Children With Biliary Atresia. *JAMA Surg* 2019; 154: 26-32 [PMID: 30208381 DOI: 10.1001/jamasurg.2018.3180]

56 Alexopoulos SP, Merrill M, Kin C, Matsuoka L, Dorey F, Concepcion W, Esquivel C, Bonham A. The impact of hepatic portoenterostomy on liver transplantation for the treatment of biliary atresia: early failure adversely affects outcome. *Pediatr Transplant* 2012; 16: 373-378 [PMID: 22463739 DOI: 10.1111/j.1399-3046.2012.01677.x]

57 Neto JS, Feier FH, Bierenbach AL, Toscano CM, Fonseca EA, Pugliese R, Candido HL, Benavides MR, Porta G, Chapaep C. Impact of Kasai portoenterostomy on liver transplantation outcomes: A retrospective cohort study of 347 children with biliary atresia. *Liver Transpl* 2015; 21: 922-927 [PMID: 25832004 DOI: 10.1002/lt.24132]

58 Sugawara Y, Makuchii M, Kaneko J, Okubo T, Mizuta K, Kawarasaki H. Impact of previous multiple portoenterostomies on living donor liver transplantation for biliary atresia. *Hepatogastroenterology* 2004; 51: 192-194 [PMID: 15011862]

59 Superina R. Biliary surgery and liver transplantation: results and thoughts for primary liver transplantation in selected patients. *Pediatr Surg Int* 2017; 33: 1297-1304 [PMID: 29036988 DOI: 10.1007/s00383-017-4174-4]

60 Diem HV, Evard V, Vhinh HT, Sokal EM, Janssen M, Otte JB, Reding R. Pediatric liver transplantation for biliary atresia: results of primary grafts in 328 recipients. *Transplantation* 2003; 75: 1692-1697 [PMID: 12777858 DOI: 10.1097/01.TP.000005658-199609000000044]

61 Fouquet V, Alves A, Branchereau S, Grabar S, Debray D, Jacquemin E, Devicor D, Durand P, Baujard C, Fabre M, Pariete D, Chardot C, Dousset B, Massault PP, Bernard D, Houssin D, Bernard O, Gauthier F, Soubrane O. Long-term outcome of pediatric liver transplantation for biliary atresia: a 10-year follow-up in a single center. *Liver Transpl* 2005; 11: 152-160 [PMID: 15666395 DOI: 10.1002/lt.20358]

62 Goss JA, Shackleton CR, Swenson K, Satou NL, Nuesse BJ, Imagawa DK, Kinkhabwala MM, Seu P, Markowitz JS, Rudich SM, McDiarmid SV, Busuttil RW. Orthotopic liver transplantation for congenital biliary atresia. An 11-year, single-center experience. *Ann Surg* 1996; 224: 276-284; discussion 284-287 [PMID: 8813256 DOI: 10.1097/00000658-199605000-00004]

63 Visser BC, Suh H, Hirose S, Rosenthal P, Lee H, Roberts JP, Hirose R. The influence of portoenterostomy on transplantation for biliary atresia. *Liver Transpl* 2004; 10: 1279-1286 [PMID: 15376306 DOI: 10.1016/j.hepat.2003.04.009]

64 Utterston EC, Shepherd RW, Sokol RJ, Bucuvalas J, Magee JC, McDiarmid SV, Anand R, Split Research Group. Biliary atresia: clinical profiles, risk factors, and outcomes of 755 patients listed for liver transplantation. *J Pediatr* 2005; 147: 180-185 [PMID: 16126046 DOI: 10.1016/j.jpeds.2005.04.073]

65 Cowles RA, Lobritto SJ, Ventura KA, Harren PA, Gelbard R, Emond JC, Altman RP, Jan DM. Timing of liver transplantation in biliary atresia-results in 71 children managed by a multidisciplinary team. *J Pediatr Surg* 2008; 43: 1605-1609 [PMID: 18778993 DOI: 10.1016/j.jpedsurg.2008.04.014]

66 Wang P, Xun P, He K, Cai W. Comparison of liver transplantation outcomes in biliary atresia patients with and without prior portoenterostomy: A meta-analysis. *Dig Liver Dis* 2016; 48: 347-352 [PMID: 26748420 DOI: 10.1016/j.dld.2015.11.021]

67 Kyoden Y, Tamura S, Sugawara Y, Yamashiki N, Matsu Y, Togashi J, Kaneko J, Kokudo N, Makuchii M. Outcome of living donor liver transplantation for post-Kasai biliary atresia in adults. *Liver Transpl* 2008; 14: 186-192 [PMID: 18236393 DOI: 10.1016/j.23144]

68 Uchida Y, Kasahara M, Egawa H, Takada Y, Ogawa K, Ogura Y, Uryuhera K, Moriohi K, Sakamoto S, Inomata Y, Kamiyama Y, Tanaka K. Long-term outcome of adult-to-adult living donor liver transplantation for post-Kasai biliary atresia. *Am J Transplant* 2006; 6: 2443-2448 [PMID: 1689600 DOI: 10.1111/j.1660-6413.2006.01487.x]

69 Samyn M, Davenport M, Jain V, Hadzic N, Joshi D, Heneghan M, Dhawan A, Heaton N. Young People with Biliary Atresia Requiring Liver Transplantation: A Distinct Population Requiring Specialist Care. *Transplantation* 2019; 103: e99-e107 [PMID: 30461724 DOI: 10.1097/TP.0000000000002553]

70 Roberts JP, Hulbert-Bearon TE, Merion RM, Wolfe RA, Port FK. Influence of graft type on outcomes after pediatric liver transplantation. *Am J Transplant* 2004; 4: 373-377 [PMID: 14961989 DOI: 10.1111/j.1660-6413.2004.00359.x]

71 Alexopoulos SP, Nekrasov V, Cao S, Groschen S, Kaur N, Genyk YS, Matsuoka L. Effects of recipient size and allograft type on pediatric liver transplantation for biliary atresia. *Liver Transpl* 2017; 23: 221-233 [PMID: 27862929 DOI: 10.1002/lt.24675]

72 Ziogas IA, Ye F, Zhao Z, Cao S, Rauf MA, Izzy M, Matsuoka LK, Gillis LA, Alexopoulos SP. Mortality Determinants in Children with Biliary Atresia Awaiting Liver Transplantation. *J Pediatr* 2021; 228: 177-182 [PMID: 32950533 DOI: 10.1016/j.jpeds.2020.09.005]

73 de Ville de Goyet Prof J, Grimaldi C Dr, Tuzzolino F, di Francesco F Dr. A paradigm shift in the
intention-to-transplant children with biliary atresia: Outcomes of 101 cases and a review of the literature. *Pediatr Transplant* 2019; 23: e13569 [PMID: 31410937 DOI: 10.1111/petr.13569]

74 **Raghu VK**, Squires JE, Mogul DB, Squires RH, McKiernan PJ, Mazariogos GV, Smith KJ. Cost-Effectiveness of Primary Liver Transplantation Versus Hepatoportoenterostomy in the Management of Biliary Atresia in the United States. *Liver Transpl* 2021; 27: 711-718 [PMID: 33460529 DOI: 10.1002/lt.25984]
