Published in final edited form as:

Curr Opin Pediatr. 2015 June ; 27(3): 389–394. doi:10.1097/MOP.0000000000000214.

Recent Advances in the Pathogenesis and Management of Biliary Atresia

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Abstract

Purpose of review—The purpose of this study is to review advances in both the pathogenesis and clinical management of biliary atresia (BA).

Recent Findings—Immunologic studies have further characterized roles of helper T-cells, B-cells, and natural killer cells in the immune dysregulation following viral replication within and damage of biliary epithelium. PROMININ-1 expressing portal fibroblasts may play an integral role in the biliary fibrosis associated with BA. A number of genetic polymorphisms have been characterized as leading to susceptibility for BA. Postoperative corticosteroid therapy is not associated with greater transplant-free survival. Newborn screening may improve outcomes of infants with BA and may also provide a long-term cost benefit.

Summary—Although recent advances have enhanced our understanding of pathogenesis and clinical management, BA remains a significant challenge requiring further investigation.

Keywords

Prominin-1; corticosteroids; portal fibroblast; portoenterostomy; rotavirus; progenitor cell

Introduction

Biliary atresia (BA) is a congenital, fibro-obliterative obstructive cholangiopathy. BA is the most common cause of pathologic direct hyperbilirubinemia.(1–3) Timely diagnosis for intervention of the disease is critical due to the rapid progression toward cirrhosis.(2, 4–6) Unfortunately, surgical drainage, the only effective intervention, is successful only half of the time.(1, 5, 6) As such, BA is the most common cause of end-stage liver disease and the leading indication for liver transplantation in children.(4) Ultimately, approximately 80% of children with BA will require one or more liver transplantations with the associated morbidity and mortality issues caused by life-long transplant-related immunosuppression. (7–11) Herein, we review recent advances in the understanding and management of BA.

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Disclosures: none

Pathogenesis of Biliary Atresia

One prominent theory regarding the pathogenesis is that bile duct injury is initially caused by a viral infection, as originally proposed by Landing (12), and then perpetuated by an autoimmune disorder. Using the established, experimental model of BA caused by perinatal inoculation of BALB/c mouse pups with Rhesus rotavirus (RRV) (13), Mohanty et al recently demonstrated the dependence of biliary destruction on rotavirus replication in cholangiocytes.(3) Hertel et al observed that passively acquired serum antibody against RRV attenuates viral replication. The authors further demonstrated that antibody is protective against RRV-induced BA and that early viral clearance is likely a critical determinant of disease.(14, 15) Nakashima et al reported that hepatobiliary pathology with inoculation of DBA/1J mouse pups with Reovirus-2 mimicks that of human BA as well as that of RRV-induced BA.(14) Past studies demonstrated the role of T-, B- and natural killer (NK) cells in the immunologic destruction of the extrahepatic bile duct in part mediated by Interferon- γ , IL-2, Tumor Necrosis Factor- α and IL-12.(16) Brindley et al showed a robust hepatic T-cell memory with significant increase in Interferon- γ in response to Cytomegalovirus (CMV) exposure, suggesting perinatal CMV exposure may be a possible initiator to BA.(17) Feldman et al recently showed that B-cell deficient mice are protected from biliary obstruction in RRV-induced BA, further validating the role of B-cells in BA pathogenesis. This may involve lack of B-cell antigen presentation and consequently impaired T-cell activation and Th1 inflammation.(18) Okamura et al found CD56⁻CD16⁺CD68⁻ NK cells were increased in damaged BA bile ducts.(19) The authors also showed that these CD16⁺ NK cells express CX3CR1, which homing them to CX3CL1 expressed by biliary epithelium. In cultured biliary epithelial cells, CX3CL1 expression can be stimulated by Toll-like receptor (TLR3) activation using a double-stranded RNA analog. Qiu et al demonstrated susceptibility to experimental RRV-induced BA may be in part due to immaturity of NK cell responsiveness and clearance of RRV-infection of cholangiocytes.(20) Okamura et al demonstrated induction of expression of the proinflammatory cytokine IL-32, which is present in the damaged bile ducts of BA patients, is induced in cultured biliary epithelial cells by synthetic viral double-stranded RNA via TLR-3 activation, Interferon- γ , and Tumor Necrosis Factor- α .(21)

Suskind et al originally described the presence of maternal microchimerism in the livers of infants with BA suggesting a potential alloautoimmune basis for the immune dysfunction seen in BA.(22) Muraji et al subsequently identified maternal chimeric CD8⁺ T-cells in the livers of BA infants.(23, 24) Interestingly, Nijagal et al identified lower rates of graft failure and retransplantation in BA recipients who received maternal donor liver compared to those who received paternal donor liver, suggesting the possibility of immune tolerance secondary to exposure to non-inherited maternal antigens.(25) Muraji recently summarized findings over the past decade regarding the theory that maternal microchimerism is the underlying cause of BA wherein the initial biliary hit is due to graft-versus-host interaction by engrafted maternal effector T-lymphocytes.(23) Ongoing analyses are essential to validate this mechanism of disease.

There continue to be notable reports of genetic polymorphisms that may predispose patient to BA. Leyva-Vega et al identified single nucleotide polymorphisms in the 2q37.3 region

associated with BA indicating that genes within this region may confer susceptibility to BA. (26) Using genome wide association studies (GWAS) of copy number variants to identify susceptibility loci in 61 BA patients, Cui *et al* recently characterized a cluster of deletions at 2q37.3 that result in deletion of one copy of *GPC1*, which encodes glypican-1, a heparan sulfate proteoglycan that regulates Hedgehog signaling and inflammation. (27) Additional functional analyses including morpholino knockdown of *gpc1* in zebrafish demonstrated a role for Hedgehog signaling in the pathogenesis of BA. Following initial GWAS, which linked mutations within the 10q24.2 locus to BA in the Han Chinese population (28), more recent analyses identified common genetic variants in the *ADDUCIN-3* gene increased the risk of developing BA. (29)

The rapidly progressing biliary fibrosis associated with BA impacts outcomes of infants with BA in terms of survival with one's native liver. (1) The principal cellular origins of collagen-producing myofibroblasts are hepatic stellate cells and portal fibroblasts. (30) Dranoff and Wells characterized isolated portal fibroblasts to demonstrate their role in a mouse model of biliary fibrosis induced by bile duct ligation (BDL). (31) Iwaisako et al recently demonstrated via cell lineage tracing studies that portal fibroblasts are the predominant precursor of myofibroblasts in BDL-induced biliary fibrosis. (32) A key pathologic intrahepatic finding of BA, which distinguishes it from other non-biliary causes of liver fibrosis, is the presence of proliferating ductular reactions, or biliary hyperplasia. These ductular reactions are typically present within regions of bridging fibrosis suggesting a potential role of these cells in the fibrogenesis of BA. These ductular reactive cells share common characteristics with epithelial progenitor and stem cells (33–36). Immunohistochemical analyses indicate that these ductular reactive cells also express both epithelial and mesenchymal markers, which has led some investigators to speculate that these ductular epithelial cells may be undergoing transdifferentiation into collagen-producing mesenchymal cells (37, 38). However, others refute the phenomenon of hepatic epithelial-mesenchymal transition (39–41). Within regions of developing BA-associated biliary fibrosis in both RRV-induced BA and human BA, there is expansion of a population of cells within and adjacent to ductular reactions, expressing the progenitor/stem cell marker PROMININ-1 along with numerous epithelial and mesenchymal markers (42). PROM1-expressing dual epithelial-mesenchymal cells also co-express *Collagen-1α* and, therefore, may contribute to the pool of portal fibroblasts.

Management of Biliary Atresia

The only effective treatment for BA is the hepato-portoenterostomy (HPE) originally described by Morio Kasai in 1959 (43, 44). This operation involves excision of the extrahepatic biliary remnant with a high portal-plate dissection in order to maximize exposure of residual bile ductules. Drainage of bile is re-established from the portal plate into a 40–50 cm Roux limb of jejunum (45) Overall, standard open Kasai is associated with jaundice clearance in 47–65% of infants, and successful biliary drainage is manifested in the stool color usually within the first postoperative week (46–48). A serum direct bilirubin of less than 2.0 mg/dL within 3 months post-Kasai is highly predictive of survival with one's native liver (1).

Given modest success rates of achieving surgical biliary drainage, efforts to improve the outcomes of BA infants span multiple levels of clinical investigation. Institutional case volume is a positive predictor of outcome for a number of complex operations (49–52). McKiernan et al reported outcomes of infants with BA undergoing HPE in the UK and Ireland during a two-year period (53). The authors reported higher rates of clearance of jaundice odds ratio 2.02 and five-year survival without transplantation 61% vs 13% in high-volume centers managing more than 5 cases per year compared to low-volume centers. These findings ultimately lead to a national directive to centralize BA management in England and Wales (54). Davenport et al subsequently reported national outcome measures for BA, which demonstrated improved native liver and overall survival rates following HPE compared to comparable countries which the authors attributed to centralization of care (55). Serinet et al reported the French experience where they observed a similarly increased native liver survival in centers with higher volume three or more HPE/year compared to lower volume centers two or fewer HPE/year (56). In contrast, Shreiber et al did not observe any improvement in post-HPE survival with native liver with higher center case volume in Canada (57).

Since earlier treatment predicts successful surgical drainage, earlier diagnosis is an important goal in efforts to significantly impact outcomes of infants with BA (1). Prenatal or newborn screening is not routine, but there is evidence of the potential benefit of screening. Harpavat et al retrospectively demonstrated that 100% of infants with BA who had serum bilirubin levels determined shortly after birth exhibited both total and direct hyperbilirubinemia (58). This suggests that serum bilirubin levels could potentially be used as a method of screening for BA. In Taiwan, where the incidence of BA is high, a universal screening program has been active since 2004 (59). Parents of all newborns are given color cards that show the spectrum of normal green stool to abnormal pale stool with the instructions to check the stool routinely and notify their pediatricians if abnormal colored acholic stool is seen. Positive results from screening resulted in additional diagnostic work-up. With Taiwanese infants, the stool color card screening program had a sensitivity of 89.7%, a specificity of 99.9%, a positive predictive value of 28.6% and a negative predictive value of 99.9% for identification of biliary atresia (60). In subsequent analyses, the authors concluded implementation of this program led to earlier diagnosis and earlier HPE 66% vs. 49% at <60 days of age, as well as improved 3-year jaundice-free survival 57% vs. 31.5% compared to a cohort historical controls (59, 61). More recently, these observations were extrapolated to two North American populations utilizing cost-effectiveness modeling.(62), (63) Both studies demonstrated significant gains in life-years as well as decreased cost of care.

Given evidence that BA is an inflammatory and potentially an autoimmune disease, immunosuppression is a logical modality of treatment of BA as it is effective for other inflammatory or autoimmune diseases (64, 65). However, results from postoperative corticosteroid use for BA use have been variable. While a number of small, nonrandomized, retrospective reports demonstrated promising improvements in biliary drainage and transplant-free survival with corticosteroids, others studies did not (66), (67), (68), (69), (70), (71), (72), (73), (74). Davenport et al reported a single center prospective, non-blinded trial, wherein a significant reduction in serum bilirubin was observed with post-HPE

corticosteroid treatment but transplant-free survival was not improved (75). A prospective, randomized trial in Japan did not demonstrate an improvement in serum bilirubin with post-HPE corticosteroids (48). Recently, the National Institutes of Health-funded Childhood Liver Disease Research Network (ChiLDReN) reported the results of a prospective, randomized, double-blinded, placebo-controlled trial of high-dose steroids in 140 post-HPE patients therapy did not result in a statistically significant difference in drainage at 6 months or transplant-free survival, although the authors noted that a small clinical benefit could not be ruled out. Importantly, steroid treatment was associated with earlier onset of serious adverse events (76).

IgG therapy has been used effectively for a number of inflammatory and autoimmune disorders including neonatal hemochromatosis (77). Hence, it has been theorized that high dose IgG therapy, which reduces secretion of pro-inflammatory cytokines and increase the number of anti-inflammatory regulatory T-cells in other autoimmune diseases (78), might be efficacious in BA in lieu of corticosteroids. Fenner et al studied the effects of high dose IgG in experimental BA in mouse pups and observed a decreased bilirubin, peribiliary inflammation, and increased ductal patency (79). The authors further observed a decrease in Vascular Cell Adhesion Molecule-1 expression, with reduced migration of immune cells to portal tracts. Importantly, high dose IgG also significantly decreased CD4⁺ and CD8⁺ T-cell production of proinflammatory cytokines and increased levels of anti-inflammatory regulatory T-cells. Currently, ChiLDReN is enrolling patients into an FDA-approved phase 1/2a clinical trial to study the safety and efficacy profiles of intravenous immunoglobulin treatment administered to infants after portoenterostomy for biliary atresia (<https://clinicaltrials.gov/ct2/show/NCT01854827>).

Recurrent cholangitis, which is thought to be the consequence of ascending bacteria colonization up the roux limb toward the portal plate, is a significant issue for most BA infants following portoenterostomy. Lee et al determined that 27 (64.3%) of 42 children experienced an average of 3.6 episodes of cholangitis with a mean length of stay of two weeks (1). Common organisms in blood culture isolates in their study included *Klebsiella pneumonia*, *Enterococcus*, *Escherichia coli* and *Pseudomonas aeruginosa*. Lien et al recently reported a pilot study in which twenty jaundice-free BA patients were prospectively randomized to receive either prophylactic neomycin or lactobacillus. Both groups experienced equivalent rates of cholangitis, which were lower than historic nontreated controls suggesting potential efficacy of lactobacillus in preventing cholangitis (80). Shneider et al reported clinically definable portal hypertension in two-thirds of 163 prospectively followed North American long-term survivors with native liver (81). Biochemical evidence of fat-soluble vitamin insufficiency is common amongst infants with BA despite supplementation (81). Over 98% of BA patients surviving more than five years with their native liver after portoenterostomy exhibit either clinical or biochemical evidence of chronic liver disease (82). A study pooling 162 patients from 14 published articles, who had survived with their native liver more than 20 years, reported that 88% (162/184) were still alive with their native liver and that 60% were experiencing liver-related complications (83). Nonetheless, survey data of BA patients surviving with their native livers indicate that their health statuses and quality of life are similar to those of their healthy peers (84).

Conclusion

Biliary atresia remains an incompletely solved puzzle. There have, however, been strides in determining the underlying pathogenesis of this neonatal fibrosing cholangiopathy. Moreover, evolution of clinical care continues with greater focus on newborn screening and suppression of the immune dysregulation associated with biliary atresia.

Acknowledgements

We thank Dr. Henri R. Ford for his encouragement and support.

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Key Points

- Genetic mutations may impact biliary organogenesis and contribute to the biliary atresia phenotype.
- Innate immunity may contribute to the destruction of the biliary epithelium that occurs in biliary atresia.
- An expanding population of cells expressing progenitor/stem cell markers within and adjacent to ductular reactions within evolving regions of biliary fibrosis may contribute to the pool of activated portal fibroblasts.
- Newborn screening of infants may improve outcomes of infants with biliary atresia and be associated with a cost benefit.
- Corticosteroid therapy following portoenterostomy do not improve survival with native liver and are associated with earlier onset of adverse side effect.