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ORIGINAL ARTICLE

HIDA, percutaneous transhepatic cholecysto-cholangiography and liver biopsy in infants with persistent jaundice: can a combination of PTCC and liver biopsy reduce unnecessary laparotomy?

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Abstract
Background Historically, HIDA is the initial diagnostic test in the evaluation of biliary atresia (BA). Non-excreting HIDA scans can yield false-positive results leading to negative laparotomy.
Objective Cholestatic infants must be evaluated promptly to exclude biliary atresia (BA) and other treatable hepatic conditions. Intraoperative cholangiogram (IOC) is the gold standard for diagnosing BA, but requires surgical intervention. Percutaneous transhepatic cholecysto-cholangiography (PTCC) and liver biopsy are less invasive and have been described in small case series. We hypothesized that PTCC and liver biopsy effectively exclude BA, thus avoiding unnecessary IOC.
Materials and methods Retrospective review of cholestatic infants who underwent PTCC, biopsy or cholescintigraphy at a tertiary children's hospital from August 1998 to January 2009. Group differences were evaluated and the receiver operator curve and safety of PTCC determined.
Results One-hundred twenty-eight cholestatic infants were reviewed. Forty-six (36%) underwent PTCC. Forty-one out of 46 (89%) had simultaneous PTCC and liver biopsy. PTCC was completed successfully in 19/23 (83%) children despite a small or absent GB on initial US. Negative laparotomy rate was 1/6 (17%) for simultaneous PTCC/liver biopsy. Complications occurred in 4/46 including bleeding (n=2), fever with elevated transaminases (n=1) and oxygen desaturations (n=1).
Conclusion PTCC, particularly when performed in combination with simultaneous liver biopsy, effectively excludes BA in cholestatic infants with acceptable morbidity. PTCC can frequently be performed when a contracted gallbladder is seen on initial US exam. Negative laparotomy rate is lowest when PTCC is coupled with simultaneous liver biopsy.

Keywords Biliary atresia · Percutaneous transhepatic cholecysto-cholangiography · Liver biopsy safety · Cholestasis · Children

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Introduction

Cholestatic infants must be evaluated promptly and efficiently to exclude treatable medical and surgical conditions. Any neonate with jaundice persisting beyond

2 weeks of age warrants investigation. Untreated BA progresses to cirrhosis and liver failure. Portoenterostomy (Kasai procedure) is unlikely to benefit infants with BA if performed after 3 months of age.

The differential diagnosis for neonatal jaundice is broad and includes congenital, acquired and inherited etiologies. Extrahepatic causes include BA, choledochal cyst, cholelithiasis, spontaneous perforation of the common bile duct (CBD) and duodenal duplication. Intrahepatic causes include Alagille and nonsyndromic bile duct paucity, neonatal sclerosing cholangitis, Bylers, idiopathic neonatal hepatitis (NH), infection, parenteral nutrition (PN) cholestasis, toxic/metabolic and endocrine disorders. Ninety percent of jaundiced infants will have either BA or NH. The differentiation between these entities can be problematic, as all imaging modalities lack complete specificity [1].

Traditionally, initial evaluation begins with a complete history and physical exam and assessment of stool color followed by laboratory tests and liver US. US signs for BA include the triangular cord sign, abnormal gallbladder morphology, lack of gallbladder contraction after oral feeding and nonvisualization of the CBD. These findings have been investigated for their diagnostic performance, which shows that they are helpful in terms of stratifying risk and aiding clinical decision-making, but they cannot stand alone for making a definitive diagnosis [2]. To confirm biliary tract patency, less invasive methods such as cholescintigraphy and duodenal aspirate evaluation have been utilized. Both are sensitive, minimally invasive options used to exclude BA, but are limited by low specificity [3–6]. Furthermore, cholescintigraphy's utility is decreased in low birth weight infants, instances of PN cholestasis or severe neonatal hepatitis, or when the total bilirubin level exceeds 10 mg/dL [4, 7]. Moreover, each test requires additional time, which may delay the diagnosis of BA and the necessary portoenterostomy beyond the optimal window of therapy [8, 9].

For a more definite diagnosis, liver biopsy is frequently utilized as a diagnostic procedure to effectively rule out BA with reported sensitivity and specificity ranging from 89% to 99% and from 82.5% to 98%, respectively [3, 8, 10–12]. Histopathological features that correlate best with BA include ductular proliferation, bile duct and ductular bile plugs, and portal fibrosis. Ductular proliferation is the most important in distinguishing BA from NH [13]. Additionally, liver biopsy may establish alternative diagnoses such as bile duct paucity or neonatal hepatitis, which may obviate the need for additional testing. However, disease processes such as PN cholestasis or alpha one antitrypsin deficiency may have histological findings similar to BA, necessitating additional tests [14, 15]. Consequently, if results of the biopsy are not definitive, demonstration of extrahepatic biliary tract patency from common bile duct to duodenum is required.

Intraoperative cholangiogram (IOC) is considered the gold standard to diagnose BA. It delineates the biliary tract, but requires surgical intervention in infants who may already be quite ill. IOC is routinely performed at our institution after biliary atresia is suggested by imaging and biopsy, and if confirmed for BA (i.e. no extrahepatic biliary duct can be visualized or cannulated), a Kasai procedure immediately follows. Due to the invasive nature of IOC, alternative tests have been utilized to exclude BA and decrease the number of unnecessary IOCs (i.e. the negative laparotomy rate). These tests include endoscopic retrograde cholangio-pancreatography (ERCP) [16–19] and percutaneous transhepatic cholecysto-cholangiography (PTCC) [20–22].

While ERCP has proved effective, relatively few pediatric centers have either the equipment or expertise to perform this procedure. Alternatively, PTCC can be performed by interventional radiologists, thus increasing this technique's availability. Recent case series of PTCC have documented the technique and its feasibility to exclude BA; however, they are limited by sample size [20, 21]. Consequently, we describe the largest single-center experience utilizing PTCC to evaluate cholestatic infants, including its diagnostic yield, and safety profile. The primary aim of this study was to determine the accuracy and safety of PTCC at excluding BA with the secondary aim of determining the "negative laparotomy rate" for PTCC with simultaneous liver biopsy, liver biopsy alone and cholescintigraphy alone.

Materials and methods

We retrospectively reviewed the charts of all cholestatic infants younger than 123 days old who underwent either cholescintigraphy, PTCC or liver biopsy as part of their initial work-up for cholestasis at Children's Hospital of Wisconsin from August 1998 through January 2009. Children with an alternative diagnosis requiring surgical intervention, such as choledochal cyst, were excluded from this study. We collected demographic information, a history of PN and acholic stools as well as laboratory values within the 1st week of diagnostic testing. We recorded the type of diagnostic procedure and biopsy results as well as the final diagnosis. The biopsy analysis focused on whether the pathologist excluded BA such that no additional diagnostic procedures were performed and not whether the biopsy results established a diagnosis of BA.

Percutaneous transhepatic cholecysto-cholangiography procedure

Each PTCC was performed as previously described [20, 21]. After informed consent, the child was moderately

sedated or placed under general anesthesia (based on provider preference) with continuous cardiorespiratory monitoring. Liver US identified the gallbladder (GB), and using real-time US guidance, a 22- or 25-gauge needle was inserted, via the right liver lobe, into the GB. Contrast agent was injected and fluoroscopic images were obtained (Figs. 1, 2, and 3). Antibiotic prophylaxis was provided at the radiologist's discretion. For each PTCC attempted (defined as an effort to cannulate the GB), we recorded whether the GB was cannulated (i.e. successful PTCC). All complications were recorded.

Percutaneous liver biopsy procedure

Liver biopsy was performed under direct ultrasound guidance with an 18-gauge core needle from an anterior subcostal approach into the right or medial left lobe of the liver. Two to three passes were generally made with a 1-cm throw length. Biopsy was performed with or without the use of a 17-gauge coaxial needle and with or without Gelfoam embolization of the tract per the interventional radiologist's preference.

Findings on percutaneous transhepatic cholecysto-cholangiography

If PTCC demonstrated extrahepatic biliary tree opacification into the duodenum (Fig. 1), the study was classified as excluding BA. A non-filled biliary tree was considered suggestive of BA (Fig. 2). Inability to cannulate the GB was considered inconclusive, but suggestive of BA, as another confirmatory test was required for diagnosis.

Cholestatic patients were followed until cholestasis resolved, death, transfer to another center or loss to follow-up.

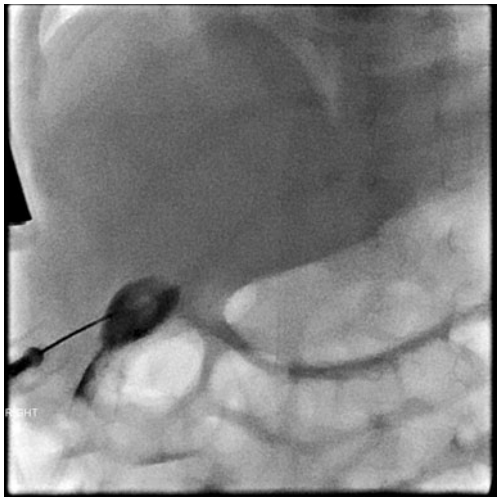

Fig. 2 Abnormal percutaneous cholecysto-cholangiography shows a small gallbladder without filling of extrahepatic ducts

Statistical methods

Sensitivity, specificity, positive and negative predictive value (PPV, NPV) with 95% confidence intervals were calculated for the initial test performed: all PTCC data, PTCC with simultaneous liver biopsy, cholescintigraphy alone or liver biopsy alone. Group differences were evaluated using the Mann-Whitney test and Fisher exact test as appropriate. Receiver operator curves (ROC) were used to graphically compare each test's true-positive and false-positive rates. Area under the curve (AUC) quantified this relationship. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA) and SPSS version 18.0. (SPSS Inc., Chicago, IL, USA). Statistical significance was defined by a P value less than 0.05. The Children's Hospital of Wisconsin institutional review board approved this study.

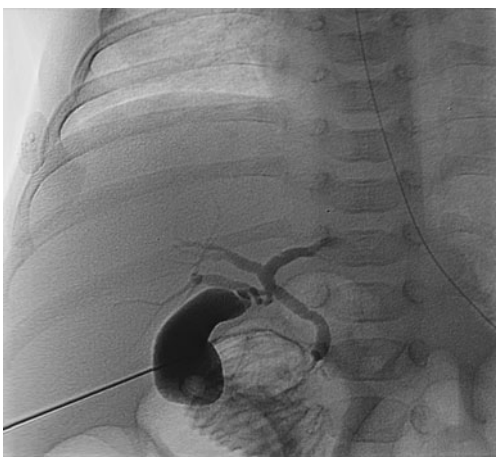

Fig. 1 Normal percutaneous transhepatic cholecysto-cholangiography shows patent intra- and extrahepatic ducts, excluding biliary atresia

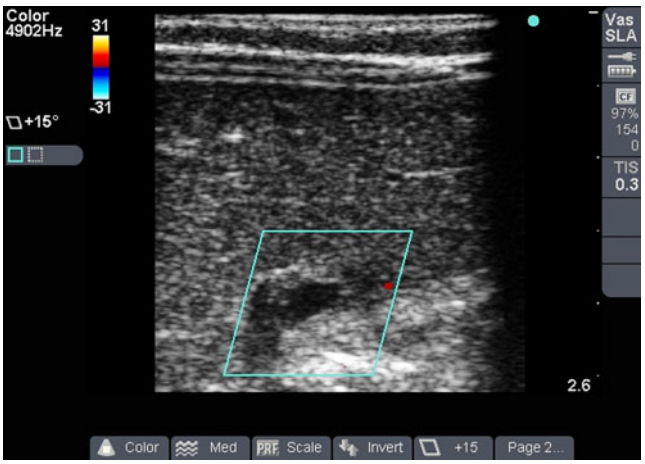

Fig. 3 Abnormal gallbladder sonogram shows a small contracted gallbladder

Results

Cholestasis was initially evaluated with cholescintigraphy alone (n=68), liver biopsy alone (n=25), or PTCC with or without simultaneous liver biopsy (n=35) in 128 infants with a median age 63 days (interquartile range [IQR] = [47–75] days). Children who underwent cholescintigraphy as the initial diagnostic test were younger (57 days-cholescintigraphy vs. 66 days-PTCC/biopsy, P=0.02), had lower alkaline phosphatase (455 IU/L-cholescintigraphy vs. 600 IU/L PTCC/biopsy, P=0.01), and an increased frequency of PN-administration (46% cholescintigraphy vs. 26 % PTCC/biopsy, P=0.03). While not clinically significant, ALT and AST were statistically lower in cholescintigraphy patients (102 and 126 IU/L vs. 143 and 180 IU/L respectively, P=0.03). Of the 128 patients evaluated, 32 (25%) were diagnosed with BA. Significant differences among children with and without BA included frequency of acholic stools, GB abnormalities and PN administration as well as serum GGT levels (all $P \leq 0.005$) (Table 1).

Percutaneous transhepatic cholecysto-cholangiography

PTCC was planned in 53/128 (41%), attempted in 46/128 (36%) and successful in 41/46 (89%). PTCC was not attempted in 7/53 (13%) because the hepatic US at the time of PTCC failed to identify a GB. Seven radiologists performed a median of 3 PTCC (range 2–16) with general anesthesia utilized in 21/46 (46%) patients.

Of the 46 attempted studies, PTCC was the initial test in 35 (76%) and 32/35 (91%) underwent simultaneous liver biopsy. For those undergoing PTCC with simultaneous liver biopsy (n=32), utilizing both PTCC appearance and pathology report from biopsy, BA was excluded in 25/32 (78%) and BA was suggested in the remaining seven. Of these seven children, six underwent IOC and BA was diagnosed in 5/6 (83%). In the one child who did not undergo IOC, cholescintigraphy was utilized because an abscess associated with recent pyloromyotomy precluded surgical intervention. For this child, tracer excretion was demonstrated on cholescintigraphy, thus excluding BA. The sensitivity, specificity and AUC for all PTCC data (i.e. with or without simultaneous liver biopsy) was 100%, 86% and 0.9, respectively. However, when we considered only those children who underwent simultaneous PTCC and liver biopsy, the sensitivity, specificity and AUC was 100%, 93% and 0.95, respectively. In the same 32 children who underwent PTCC with simultaneous liver biopsy, biopsy results alone would have excluded BA in 20/32 (63%), suggesting that 12/32 (38%) children would have required surgical evaluation to effectively rule out BA. Table 2 demonstrates the diagnostic values of each initial test.

Complications occurred in 4/46 (8.7%) children who underwent PTCC with or without simultaneous liver biopsy. Two children developed bleeding of the biopsy site; one of them required surgical intervention. The second developed hemobilia, which resolved without intervention or transfusions. One child had elevated transaminases and fever after isolated PTCC. Blood cultures were negative and the child was discharged after 48 h. Finally, one child experienced an episode of self-resolving oxygen desaturation after simultaneous PTCC and liver biopsy. This was related more to the sedation/anesthesia and could be excluded.

Liver US

Liver US was performed in all children. The GB was absent in 17/128 (13%) and described as small or contracted in 63/128 (49%). PTCC was successfully performed in 16/19 (84%) children with a small/contracted GB on initial US and 3/17 (18%) children with no GB visualized on initial US. For the 17 children with an initially absent GB, repeat US at the time of liver biopsy identified a GB in four

Table 1 Initial patient characteristics (data presented as count [%] or median [IQR])

	BA (n=32)	No BA (n=96)	P-value
Male	14 (43.8%)	61 (63.5%)	0.06
Age at 1st test (days)	59 (41–71)	64 (47–79)	0.20
Weight (kg)	4.71 (4.09-5.03)	3.85 (3.05-4.33)	< 0.0001
Documented acholic stools	23 (72%)	28 (33%)	0.0003
History of PN	3 (9.4%)	42 (46%)	0.0002
Small or absent GB	27 (84%)	53 (55%)	0.005
Total bilirubin (mg/dL)	7.1 (6.0-8.5)	6.6 (5.0-8.4)	0.39
Conjugated bilirubin (mg/dL)	3.8 (3.3-4.6)	3.5 (2.5-5.0)	0.26
ALP (IU/L)	578 (473–800)	493 (388–679)	0.12
GGT (IU/L)	755 (368–971)	215 (106–357)	< 0.0001
ALT (IU/L)	110 (79–170)	112 (76–170)	0.93
AST (IU/L)	177 (112–216)	164 (109–223)	0.88

IQR interquartile range, *BA* biliary atresia, *kg* kilograms, *PN* parenteral nutrition, *GB* gallbladder, *ALP* alkaline phosphatase, *GGT* gamma glutamyl transferase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

Table 2 Diagnostic values of the utilized initial tests listed as percentage (95% CI)

Test	Sensitivity (%)	Specificity (%)	AUC[a]	PPV (%)	NPV (%)	Negative IOC[b]
All PTCC data (n=35)	100 (52–100)	86 (67–96)	0.90±0.1	60 (27–86)	100 (83–100)	‡
PTCC + Biopsy (n=32)	100 (46–100)	93 (74–99)	0.95±0.07	71 (30–95)	100 (83–100)	1/6 (17%)
Biopsy alone (n=28)	100 (56–100)	83 (58–96)	0.75±0.19	70 (35–92)	100 (75–100)	3/9 (33%)
Cholescintigraphy (n=68)	95 (72–100)	57 (42–71)	0.60±0.27	46 (30–63)	97 (80–100)	6/18 (33%)

CI confidence interval, *AUC* area under the curve, *PPV* positive predictive value, *NPV* negative predictive value, *IOC* intraoperative cholangiogram, *PTCC* percutaneous transhepatic cholecysto-cholangiogram

[a] AUC presented as value ± standard error of mean

[b] negative IOC patients who underwent a surgical evaluation after an initial test and were found not to have BA

‡ negative laparotomy rate not calculated for 3 children who underwent isolated PTCC as initial test

children allowing PTCC to be completed successfully in three, excluding BA in two and suggesting BA in one, which was confirmed surgically. For the remaining child-where the GB was identified but in whom PTCC was unsuccessful, IOC confirmed BA.

Liver biopsy

Liver biopsy was performed in 105/128 (82%) children and was the initial test in 25 (20%). The sensitivity, specificity and AUC for liver biopsy alone were 100%, 83%, and 0.75, respectively. In 9 children, although liver biopsy suggested obstruction, IOC was performed and BA was excluded in 3, resulting in a negative laparotomy rate of (3/9) 33%. Table 3 shows the final diagnoses in all children.

Cholescintigraphy

Cholescintigraphy was utilized initially in 68/128 (53%) children and demonstrated normal uptake and excretion in 29/68 (41%). Initial scintigraphy inappropriately demonstrated tracer excretion in one child, who was eventually diagnosed with BA. The sensitivity, specificity and AUC for cholescintigraphy alone were 95%, 57% and 0.60, respectively. Eighteen children underwent surgical evaluation directly following non-excreting scans and BA was excluded in six, resulting in a negative laparotomy rate of 6/18 (33%).

In ten children with non-excreting cholescintigraphy, PTCC with simultaneous liver biopsy was utilized in nine cases while PTCC alone was performed on the remaining child. In the nine infants, BA was excluded in eight (89%) thereby avoiding IOC. For these same eight children, retrospectively, the histopathology from the liver biopsy alone would have excluded BA in only 50% of cases, thus necessitating the information obtained from PTCC to avoid surgical evaluation in the remaining 50% of cases. For the remaining child who underwent PTCC and simultaneous liver biopsy, PTCC suggested BA, which was confirmed by IOC. In the single case where PTCC was performed alone, no child for whom PTCC successfully excluded BA was ever diagnosed with BA.

Discussion

Our study, the largest reported pediatric series utilizing PTCC, demonstrates that PTCC provides additional, valuable diagnostic information when evaluating cholestatic infants. The greatest yield occurs when liver biopsy and PTCC results are utilized jointly with an AUC of 0.95 compared to 0.9 for all PTCC data, 0.75 for liver biopsy alone or 0.60 for cholescintigraphy alone (Fig. 4). Additionally, the negative laparotomy rate was 17% for simultaneous PTCC and liver biopsy compared to 33% for either cholescintigraphy alone or liver biopsy alone.

The complication rate of 8.7% for children undergoing PTCC, with or without liver biopsy is comparable to reported literature values of 7.6-9% in similar age infants with or without US guidance [23, 24]. Furthermore, all three approaches are similar to the 12% complication rate reported for diagnostic laparoscopy [25]. For the two infants with bleeding complications from the procedure, there was no way to determine whether it was secondary to the PTCC or the liver biopsy. Finally, we demonstrated that even in children with a contracted GB on initial US, PTCC may be successfully performed in a majority 16/19 (84%) of cases.

Review of the literature, although limited, has demonstrated similar diagnostic efficacy with PTCC. In one report, 9/15 children underwent PTCC for cholestasis and suspected BA during a 2-year period. All nine children had a GB visualized on US, but failed to demonstrate radiotracer excretion on cholescintigraphy. For five of the nine children (56%), PTCC excluded BA, while PTCC was suggestive of BA in three and suggestive of biliary hypoplasia in one [20]. In a second series, PTCC effectively excluded BA in 9/35 cholestatic infants. The remaining 26

Table 3 Final diagnoses of cholestatic patients (n=128) who underwent biopsy, scintigraphy or PTCC

Diagnosis	Count (%)
Neonatal hepatitis-idiopathic	33 (25.8%)
Biliary atresia	32 (25.0%)
PN-cholestasis	27 (21.1%)
α-1 antitrypsin deficiency	8 (6.3%)
Alagille syndrome	6 (4.7%)
Cytomegalovirus infection	5 (3.9%)
Inspissated bile syndrome	5 (3.9%)
Panhypopituitarism	3 (2.3%)
Sepsis	2 (1.6%)

Cystic fibrosis, Gaucher, ischemic hepatitis, lupus, paucity-NOS, paucity-trisomy 21, sclerosing cholangitis (n=1 each) *PN* parenteral nutrition, *NOS* not otherwise specified

underwent intraoperative evaluation due to an abnormal GB on US, coagulopathy or intercurrent sepsis [21]. These reports suggest that PTCC is helpful in excluding BA and preventing unnecessary surgical intervention despite cholescintigraphy result suggestive of BA, especially when a normal GB is present on initial US.

Although PTCC may effectively exclude BA, liver biopsy remains essential in evaluating cholestatic infants for the distinctive information it provides in identifying potential alternative diagnoses [3, 8, 10, 11]. Although the specificity of liver biopsy in our series for diagnosing BA was lower than frequently reported values [3, 8, 10–12], it coincides with a recent abstract from the Biliary Atresia Research Consortium (BARC) documenting the challenges of biopsy interpretation. The abstract demonstrated only moderate interobserver agreement for the diagnosis of BA (kappa=0.52-0.65) with a diagnostic accuracy of 57-93% when pathologists had to exclude obstruction (i.e. BA) in the face of neonatal hepatitis [26]. Consequently, it is in these children without BA, but in whom biopsy alone is unable to exclude obstruction for whom PTCC is most beneficial.

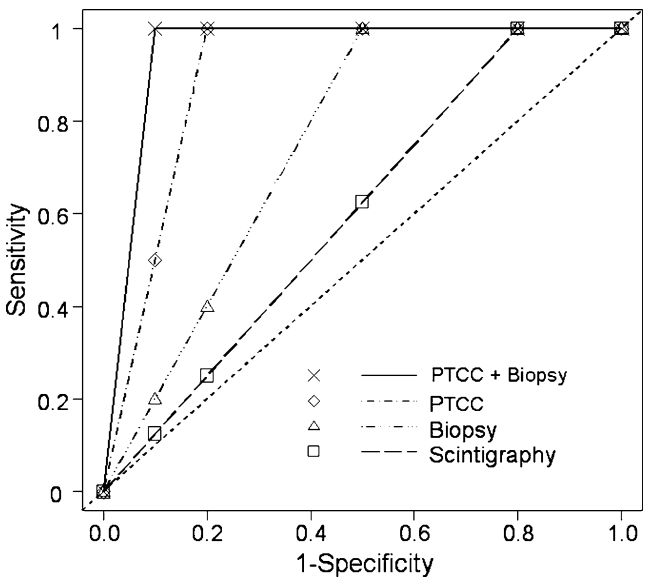

Fig. 4 ROC curve for different diagnostic tests

One potential concern with utilizing the simultaneous approach of PTCC and liver biopsy is that PTCC may be performed unnecessarily in children in whom biopsy alone would exclude BA. However, based on our experience, not only was safety not compromised by the additional procedure, but specificity significantly increased from 79% with liver biopsy alone to 93% with both liver biopsy and PTCC. Furthermore, the combined PTCC and liver biopsy data resulted in the lowest negative laparotomy rate of all three procedures utilized as the initial diagnostic test. Last, although not a primary end point of this study, the direct cost associated with simultaneous PTCC and liver biopsy was significantly less than the charges associated with IOC. Nevertheless, the cost-effectiveness of PTCC or, for that matter, any diagnostic test must not only include evaluation of direct risks from undergoing invasive procedures, but also the impact of unnecessary interventions resulting from a false-positive test, including family impact and length of hospitalization. Future studies are therefore warranted to identify children most likely to benefit from simultaneous PTCC and liver biopsy, as well as to perform a comprehensive evaluation of the cost-effectiveness of this tandem approach.

A benefit of PTCC not mentioned to this point is the potential therapeutic effect of "flushing through" inspissated bile plugs and casts during the procedure. Accelerated resolution of cholestasis in infants without BA has been described in the literature [27].

It should be noted that antibiotic prophylaxis for percutaneous biliary procedures is recommended by the Society of Interventional Radiology guidelines. The one infant who developed a fever after the PTCC did not receive antibiotics. The variable use of antibiotics before PTCC in this retrospective study was based on the preferences of the interventional radiologist performing the procedure [28].

Based on the review of our data, we believe simultaneous PTCC and liver biopsy has greater sensitivity and specificity for diagnosing BA than HIDA or biopsy alone. Accordingly, we recommend infants between 2 weeks and 6 weeks of age with persistent cholestasis by lab work undergo US and testing to exclude an alternative diagnosis to BA. If no alternative diagnosis to BA is identified, we recommend proceeding to PTCC and liver biopsy, with HIDA scan as an acceptable optional study to be performed first. If HIDA is performed and shows excretion to bowel,

PTCC and liver biopsy are not required. For infants older than 6 weeks of age, we believe the delay in diagnosing and treating BA precludes the use of HIDA, and recommend proceeding directly to PTCC and liver biopsy.

Limitations of our study include its retrospective design, which inherently leads to missing data; this is especially important when evaluating the presence of acholic stools, a major predictor of true biliary obstruction. Second, it is impossible to discriminate whether the inability to cannulate the GB was due to technical reasons or the challenge of inserting a needle into a small target. Nevertheless, multiple radiologists with variable interventional experience successfully performed PTCC in our series. Additionally, the impact of having multiple pathologists, instead of a designated hepatopathologist, could also affect diagnostic accuracy. As demonstrated in the BARC abstract, each physician has a different threshold at which he or she will exclude a serious diagnosis such as biliary atresia. Thus, knowledge of each center's relative strengths and resources may need to be factored into the choice of which tests to use to best exclude BA.

Conclusion

Percutaneous transhepatic cholecysto-cholangiography has an acceptable risk profile and effectively excludes biliary in cholestatic infants. Simultaneous percutaneous transhepatic cholecysto-cholangiography and liver biopsy increases specificity yielding the lowest negative laparotomy rate in comparison to other standard forms of diagnostic testing. If initial US demonstrates a small or contracted gallbladder, BA should not be entirely excluded. Future studies should focus on identifying children in whom percutaneous transhepatic cholecysto-cholangiography with or without simultaneous liver biopsy is most likely to be helpful, as well as comprehensively evaluate the cost-effectiveness of this tandem approach.

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