

# Cholestasis In Infants With Down Syndrome Is Not Due To Extrahepatic Biliary Atresia: A Ten-Year Single Egyptian Centre Experience

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Magd A Kotb <sup>1</sup>  
Iman Draz<sup>1</sup>  
Christine WS Basanti <sup>1</sup>  
Sally TM El Sorogy<sup>2</sup>  
Hesham M Abd Elkader <sup>3</sup>  
Haytham Esmat<sup>4</sup>  
Hend Abd El Baky<sup>1</sup>  
Dalia Sayed Mosallam<sup>1</sup>

<sup>1</sup>Pediatrics Department, Faculty of Medicine, Kasr Al Ainy, Cairo University, Cairo, Egypt; <sup>2</sup>Pediatrics Department, Public Mounira Hospital, Cairo, Egypt; <sup>3</sup>Department of Pediatric Surgery, Faculty of Medicine, Ain Shams University, Cairo, Egypt; <sup>4</sup>Department of Pediatric Surgery, Cairo University, Cairo, Egypt

**Purpose:** We aimed to define the clinical presentations, course and outcome of cholestasis in infants with Down syndrome (trisomy 21) who presented to the Pediatric Hepatology Clinic, New Children Hospital, Cairo University, Egypt.

**Methods:** Retrospective analysis of data of cohort of infants with Down syndrome and cholestasis who followed up during 2005–2015.

**Results:** Among 779 infants with cholestasis who presented during 2005–2015, 61 (7.8%) had Down syndrome. Six dropped out. Among the 55 who followed-up for a mean duration  $\pm$ SD = 12.1  $\pm$  16.7 months, none had extrahepatic biliary atresia (EHBA), 37 (63.3%) had neonatal hepatitis and 18 (32.7%) had non-syndromic paucity of intrahepatic biliary radicals. Fourteen (25.4%) had associated congenital heart disease. Only 35 (63.3%) cleared the jaundice. Twenty-nine (52.7%) received ursodeoxycholic acid (UDCA); of them, 13 cleared the jaundice, one improved, 14 progressed and one died, compared to 22 who cleared the jaundice of the 26 who did not receive UDCA. Only three of those who did not receive UDCA progressed and none died. UDCA carried a 3.4-fold risk of poor prognosis ( $p$  = 0.001). UDCA use was associated with more complications ( $p$  = 0.016) in those with Down syndrome and cholestasis.

**Conclusion:** We did not come across EHBA among neonates and infants with Down syndrome in 10 years. Non-syndromic paucity is associated with favorable outcome in infants with Down syndrome. UDCA use in cholestasis with Down syndrome is associated with poor outcome.

**Keywords:** cholestasis, extrahepatic biliary atresia, EHBA, neonatal hepatitis, Down syndrome, trisomy 21, ursodeoxycholic acid, UDCA

## Introduction

Down syndrome (trisomy 21) is associated with congenital anomalies in 64% of cases. The cardiac anomalies are commonest, followed by digestive system, musculoskeletal system, urinary system, respiratory and other system anomalies.<sup>1</sup> Estimated worldwide incidence of Down syndrome is 1:1,000–1:1,100, 0.827:1000 in USA<sup>2</sup> and 1.8:1000–1.6:1000 in Egypt.<sup>3</sup> Cholestasis was reported to affect 3.9% of neonates and infants with Down syndrome in a population-based study.<sup>4</sup> The cholestasis in Down syndrome was reported to be due to the probability of a smaller circulating bile acid pool size, a lower rate of synthesis, reduced recirculation of bile acids and immature function of the canalicular bile acid transporting system.<sup>5</sup> The increased susceptibility of cholestasis in Down syndrome was not mapped to

Correspondence: Dalia Sayed Mosallam  
Pediatrics Department, Faculty of  
Medicine, Cairo University, Al Manial,  
Cairo 11562, Egypt  
Tel +20 2 33386592  
Email daliamosallam@kasralainy.edu.eg

chromosome 21, i.e. major genes controlling the uptake, synthesis, or secretion of bile acids in human hepatocytes, synthesis, or ileal enterocytes.<sup>6</sup> The aim of this study was to define the spectrum of clinical presentations, course and outcome of cholestasis in infants with Down syndrome.

## Subjects And Methods

### Subjects

This is an observational study that included a retrospective analysis of data of a cohort of infants with Down syndrome and cholestasis who followed up during 2005–2015 at the Pediatric Hepatology Clinic, New Children Hospital, Cairo University, Egypt. The study was approved by the Pediatric Department Committee for Post-Graduate Studies and Research, and by the Post-Graduate Studies and Research Administration, Faculty of Medicine, Cairo University, Egypt. Parental approval was not applicable to this retrospective, observational, non-interventional cohort study.<sup>7</sup> The study complies with the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects.<sup>8</sup>

### Methods

We revised all files of neonates and infants who presented with cholestasis and clinical features of Down syndrome (trisomy 21) during 2005–2015. We analyzed all data of recruited children, including the history of age at onset of symptoms, age at presentation, presenting symptom, complications and/or associations of liver disease, neurologic disease, age of the patient at the time of the study, weight and height percentiles, and outcome. Anthropometric measures were plotted against Egyptian percentiles for children with Down syndrome weight and height<sup>3</sup> and recorded as percentiles for age.

Etiology of cholestasis was studied according to clinical judgment, i.e., virology, bile acids, metabolic screen, imaging and liver biopsy.

The outcome was graded into resolved, improved, stationary, progressive and death. The resolved outcome was when the cholestasis resolved without sequelae; improved, with an improvement of cholestasis but did not resolve completely; stationary was coined to those who did not improve or deteriorate; while progressive was coined to those where cholestasis increased.

### Statistical Analysis

All the statistical analyses in this study were conducted using the Statistical Package for Social Sciences version 19 (SPSS,

Chicago, IL). Simple frequency, cross-tabulation, descriptive analysis, tests of significance (*t*-test for parametric data and  $\chi^2$  tests for non-parametric numbers  $N \leq 5$ ), and correlations were employed.

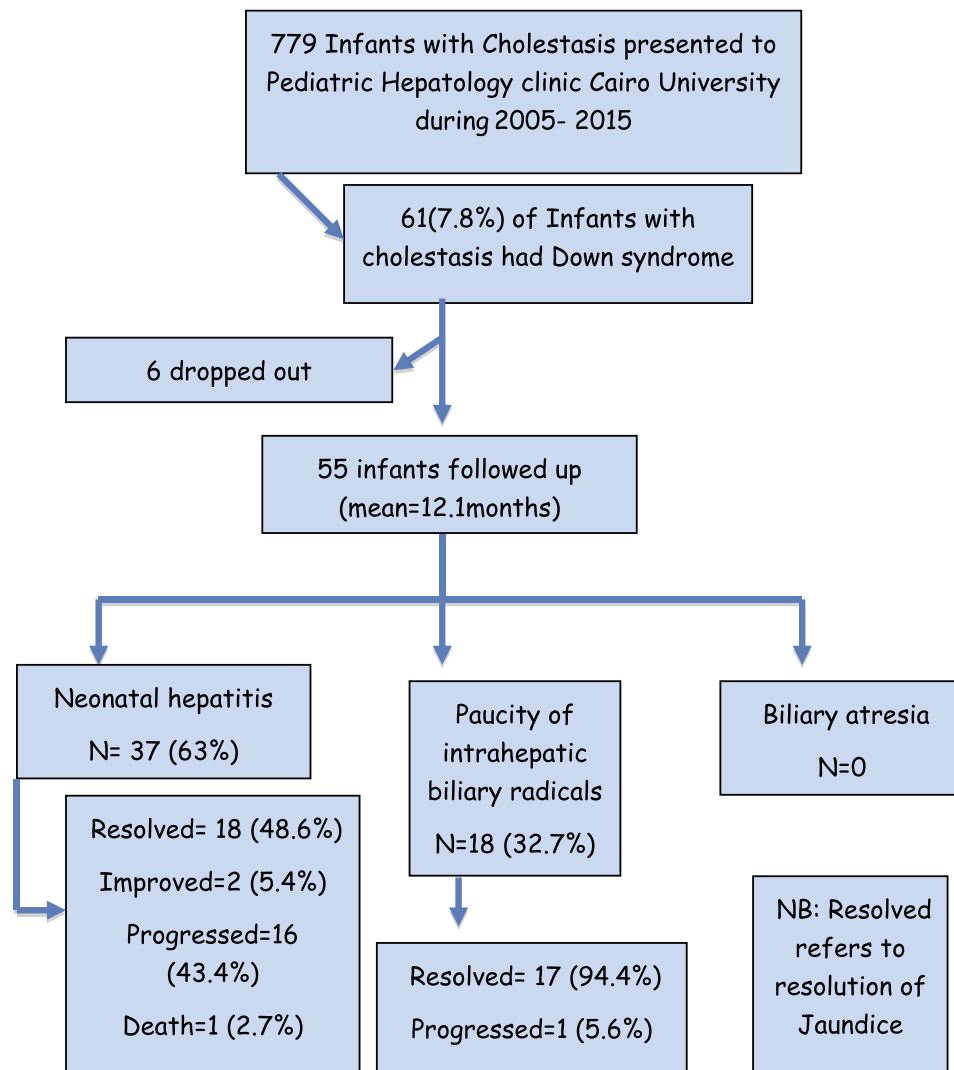
## Results

During 2005–2015 only 61 infants with Down syndrome presented to the Pediatric Hepatology Clinic, Cairo University. Six (9.2%) dropped out and did not show up for a second visit; they were all females (Figure 1). The other 55 were followed up for  $12.1 \pm 16.7$  months. Of them, 28 (51%) were females and 27 (49%) males. Mean  $\pm$  SD age at onset of cholestasis was  $1.23 \pm 11.78$  months, and at presentation to our medical attention was  $2.1 \pm 9.2$  months. Seventeen (30.1%) were the product of a consanguineous marriage. Fifteen (27.3%) had a history of another family member affected by cholestasis. The symptoms, signs of the studied cohort, their serum bilirubin and liver enzymes are shown in Tables 1 and 2, respectively. Liver biopsy was performed in 32 (58.2%) subjects and the findings are shown in Table 2.

Associated congenital cardiac anomalies were encountered in 14 (25.4%) children (Table 1). No other anomalies were encountered in our studied cohort. None had any bone marrow-associated disease.

Etiology and outcome of cholestasis in the studied cohort of neonates and infants with down syndrome are shown in Figures 2 and 3, respectively.

None of the affected infants had EHBA, 37 (67.3%) had neonatal hepatitis and 18 (32.7%) suffered from non-syndromic paucity of intrahepatic biliary radicals. Cholestasis resolved in 35 (63.6%). None tested positive for viral screening known to cause neonatal hepatitis or metabolic workup and none had progressive familial intrahepatic cholestasis (Figure 2). One child had massive fibrosis, with unidentified underlying pathology, suggesting congenital hepatic fibrosis. Figure 1 depicts the diagnosis and outcome of the studied cohort. They all received fat-soluble vitamin supplements and 29 (52.72%) received UDCA also. Of them, 21 (72.4%) suffered from complications. Both those who received UDCA and those who did not were matched as regards severity of cholestasis ( $p=0.17$ ). UDCA use was associated with poorer outcome ( $p=0.000$ ) and complications ( $p=0.016$ ) (Table 3). UDCA in neonates with Down syndrome and cholestasis carried a 3.4-fold risk of poor prognosis ( $p=0.001$ ) (95% confidence interval) (Figure 3).



**Figure 1** Flowchart of studied cohort of neonates and infants with Down syndrome and cholestasis.

## Discussion

During 2005–2015, 7.8% of the neonates and infants who presented with cholestasis to the Pediatric Hepatology Clinic, Faculty of Medicine, Cairo University had the Down syndrome (trisomy 21) phenotype. Clinically, cholestasis was mostly without organomegaly, where only 36.5% and 40% had hepatomegaly and splenomegaly, respectively. The outcome was generally favorable unless UDCA was given.

### Congenital Heart Disease Was Encountered In Only 25% Of Cases And None Had Cyanotic Heart Disease

Down syndrome is associated with congenital heart disease (CHD) in 40–60%,<sup>9–11</sup> with a dramatic increase from

about 20% in the early 1970s to more than 50% in the late 1980s ( $p = 0.0001$ ) in certain areas.<sup>12</sup> In Egypt, studies of the prevalence of CHD in Down syndrome are limited, but the reported range was almost 40%.<sup>13,14</sup> It is not clear why our cohort had less CHD compared to other populations of Down syndrome. More studies are required to establish or refute a protective effect of placental metabolism of environmental factors that are responsible for the development of CHD in a developing fetus with Down syndrome and/or cholestasis. The sample size is small, however, to draw sound conclusions, yet it remains an observation that CHD is less prevalent among Down syndrome with cholestasis, and the CHD spectrum did not include cyanotic heart disease.

**Table 1** Clinical Findings In Down Syndrome Cohort With Cholestasis

		Number Of Affected Children	Percent
Vomiting	Present	2	3.6
	Absent	53	96.4
Diarrhea	Present	1	1.8
	Absent	54	98.2
Abdominal Distension	Present	22	40
	Absent	3	5.5
Sepsis	Present	1	1.8
	Absent	54	98.2
Dark Urine	Present	25	45.5
	Absent	30	54.5
Clay-Colored Stools	Present	8	14.5
	Absent	47	85.5
Pruritus	Present	6	10.9
	Absent	49	89.1
Scratch Marks	Present	7	12.7
	Absent	48	87.3
Hepatomegaly	Present	20	36.36
	Absent	35	63.6
Splenomegaly	Present	22	40
	Absent	33	60
Cardiac Anomalies	PFO	3	5.5
	ASD	3	5.5
	VSD	2	3.6
	Combined ASD + VSD	6	10.9
	Total	14	25.5
	Absent	41	74.5

## We Did Not Come Across A Single Case Of EHBA In Down Syndrome During The 10 Years 2005–2015

This comes in congruence with previous literature, as we failed to find any previous reports of Down syndrome associated with EHBA. Kotb recently defined EHBA as aflatoxin-induced cholangiopathy in neonates with GST M1 null deficiency,

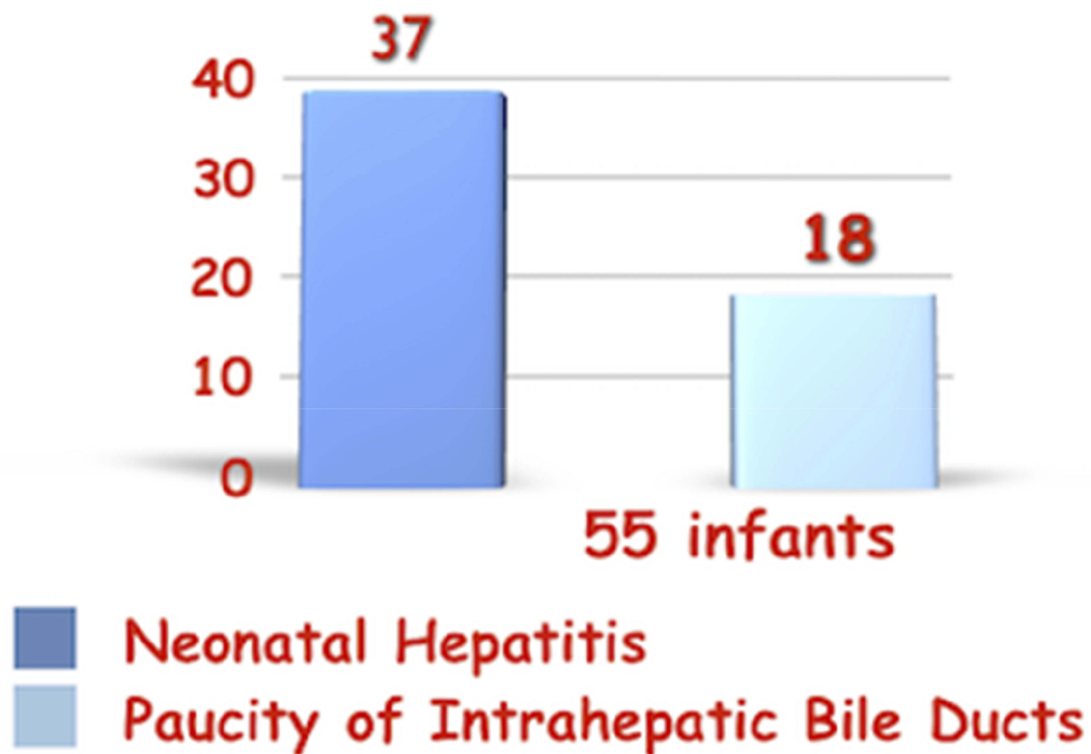
**Table 2** Laboratory And Liver Biopsy Findings In Down Syndrome Cohort With Cholestasis

<b>Laboratory Findings</b>			
		Range	Mean ± SD
Total bilirubin (mg%)		4–10.7	6.48± 1.81
Direct bilirubin (mg%)		3–9.7	4.1± 1.67
ALT		0.65–18.15	5.45± 3.99
AST		0.97–26.21	7.55± 5.14
<b>Liver Biopsy Findings in 32 Children</b>			
		Number	Percent
Hepatocytes	Normal	7	21.9
	Diffuse Ballooning	25	78.1
Infiltration by Inflammatory Cells	Present	28	87.5
	Absent	4	12.5
Bile Duct Proliferation	Present	23	71.8
	Absent	9	28.1
Paucity of Intrahepatic Biliary Radicals	Present	18	56.26
	Absent	14	43.75
Kupffer Cells (Stellate Macrophages)	Normal	11	20
	Hyperplastic	21	38.2
Architecture	Intact	32	100
	Distorted	0	0
Fibrosis	Present	2	6.25
	Absent	30	93.75
Hepatic Veins	Normal	5	15.62
	Distended	27	84.37

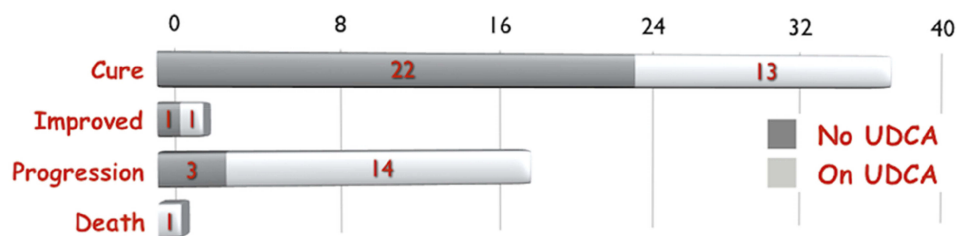
**Note:** ALT and AST were calculated in folds of the upper level of normal.

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; Number, number of affected children; SD, standard deviation.

while damage to bile ducts was mediated through neutrophil elastase. Damage control of the aflatoxin-induced cholangiopathy through neutrophil elastase ends in fibrosis and obliteration of extrahepatic bile ducts.<sup>15</sup> Factors involved in the etiology of EHBA were not sought in this cohort, i.e., aflatoxins, glutathione *S* transferase M1, p53 and neutrophil functions. It seems that Down syndrome protects against the development of biliary atresia. This protective role might be due to compromised neutrophil function in Down syndrome,<sup>16,17</sup> which might arrest the inflammatory process of EHBA.



**Figure 2** Etiology of Cholestasis in Down syndrome. None had biliary atresia.



**Figure 3** The outcome of Cholestasis in Down syndrome. UDCA use was associated with poor outcome ( $p=0.000$ ).

### Paucity Of Intrahepatic Biliary Radicals Has Excellent Prognosis In Down Syndrome

Generally, paucity of intrahepatic biliary radicals has a 69% chance of clearance of cholestasis in absence of UDCA intake,<sup>18</sup> yet 94.4% of our cohort of neonates and infants with Down syndrome with paucity of intrahepatic biliary radicals cleared the cholestasis. Again, it seems that Down syndrome enhances clearance of cholestasis. This effect could be attributed to the compromised immunity in Down syndrome; this compromise will not mount massive destructive effect in the cholestasis inflammatory process.<sup>19</sup>

### We Could Not Identify The Etiology Of Neonatal Hepatitis In Down Syndrome

The etiology of cholestasis of all of our studied neonates and infants with Down syndrome was idiopathic hepatitis, despite undergoing the battery of investigations to identify etiology (metabolic, congenital and infectious) when appropriate according to clinical situation.<sup>18</sup> The etiology of neonatal cholestasis in our studied cohort remained idiopathic, with no overlap in etiology. We did not come across any cases of cystic fibrosis, infections, or galactosemia or any other etiology in our cohort with Down syndrome.

**Table 3** Outcome And Associated Complications Of The Cohort With Down Syndrome And Cholestasis According To Etiology, UDCA Intake And Association Of Congenital Heart Disease

Outcome					Pvalue
According to Etiology of Cholestasis					
		Hepatitis N= 37	PIBD N= 18		
Resolved Cholestasis	35	18	17	0.012	
Improved	2	2	0		
Progression	17	16	1		
Death	1	1	0		
According to Intake of UDCA					
		Received UDCA N= 29	No UDCA N= 26		
Resolved Cholestasis	35	13	22	0.016	
Improved	2	1	1		
Progression	17	14	3		
Death	1	1	0		
Associated Cardiac Anomaly					
		Yes N= 14	None N= 41		
Resolved Cholestasis	35	6	29	0.215	
Improved	1	1	0		
Progression	17	7	10		
Death	1	0	1		
Complications in Studied Cohort of Down Syndrome					P
	Total	Received UDCA N= 29	No UDCA N= 26		
Recurrent Diarrhea	Yes	10	10	0	0.001
	None	45	19	26	
	Total	55	29	26	
Otitis Media	Yes	2	2	0	0.2
	None	53	27	26	
	Total	55	29	26	
Pneumonia	Yes	6	6	0	0.016

(Continued)

**Table 3** (Continued).

Outcome					Pvalue
	None	49	23	26	
	Total	55	29	26	
Bronchitis	Yes	9	0	9	0.002
	None	20	26	46	
	Total	29	26	55	
Intractable Pruritus	Yes	1	0	1	0.33
	None	28	26	54	
	Total	29	26	55	

**Note:** All neonates with congenital cardiac anomaly had neonatal hepatitis.

## UDCA Is Not Effective And Is Not Safe In Cholestasis In Down Syndrome

UDCA was found to be ineffective in clearing cholestasis in neonates and infants with Down syndrome, and its use was associated with significantly worse outcome. UDCA compromised the outcome of those with Down and cholestasis – only 44.8% of those who received UDCA resolved the cholestasis, compared to 84.6% of those who did not receive UDCA. UDCA generally impedes resolution of cholestasis in neonatal hepatitis compared to no UDCA (44.8% compared to 70.2%, respectively).<sup>18</sup> The discouraging effect of UDCA is exaggerated in our studied cohort. It is not clear why UDCA is more toxic in neonates with Down syndrome and cholestasis. The UDCA toxicity in cholestasis in Down syndrome might be attributed to their compromised detoxification of medications, e.g., methotrexate, glucocorticoids, anthracyclines, etc.<sup>20</sup> It might be related to trisomy 21 type karyotyping or other genetic makeup that needs further investigation.

## Conclusion

Cholestasis complicates Down syndrome. We did not come across EHBA among our studied cohort in 10 years. Down syndrome seems to protect against the development of EHBA. Use of UDCA in cholestasis associated with Down syndrome compromises resolution of cholestasis and its use is associated with poor prognosis. UDCA use in cholestasis associated with Down syndrome should be contraindicated.

## Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHD, congenital heart disease; D.Bil, direct bilirubin; EHBA, extrahepatic biliary atresia; SD, standard deviation; T.Bil, total bilirubin; UDCA, ursodeoxycholic acid.

## Compliance With Ethical Statements

This article does not contain any studies with human participants or animals performed by any of the authors. It is a retrospective study including all files of neonates and infants who presented with cholestasis and clinical features of Down syndrome (trisomy 21) during 2005–2015. The study was approved by The Pediatric Department Committee for Post-Graduate Studies and Research, and by Post-Graduate Studies and Research Administration, Faculty of Medicine, Cairo University, Egypt.

## What Is Known?

1. Exclusion of surgical causes of cholestasis is invasive, yet it is part of workup in every neonate with cholestasis as surgical portoenterostomy should not be delayed beyond 3 months of age to halt the march of biliary cirrhosis.
2. Cholestasis associated with trisomy 21 (Down syndrome) has been reported previously.

## What Is New?

1. Cholestasis in Down syndrome was never found to be due to biliary atresia; we did not come across a single obstructive cholestasis in Down syndrome in 10 years of practice.
2. Generally, the outcome of cholestasis is favorable in Down syndrome, especially if the etiology of cholestasis is non-syndromic paucity, unless they receive ursodeoxycholic acid, as its' use is associated with poor outcome, complications and fatality.

## Acknowledgments

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to all of the data and takes full responsibility for the veracity of the data and statistical analysis.

## Disclosure

The authors report no conflicts of interest in this work.

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