Management of Neonatal Cholestasis: Consensus Statement of the Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics

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Justification*:* Neonatal cholestasis is an important cause of chronic liver disease in young children. Late referral and lack of precise etiological diagnosis are reasons for poor outcome in substantial number of cases in India. There is a need to create better awareness among the pediatricians, obstetricians and primary care physicians on early recognition, prompt evaluation and referral to regional centers.

Process: Eminent national faculty members were invited to participate in the process of forming a consensus statement. Selected members were requested to prepare guidelines on specific issues, which were reviewed by two other members. These guidelines were then incorporated into a draft statement, which was circulated to all members. A round table conference was organized; presentations, ensuing discussions, and opinions expressed by the participants were incorporated into the final draft.

Objectives*:* To review available published data on the subject from India and the West, to discuss current diagnostic and management practices in major centers in India, and to identify various problems in effective diagnosis and ways to improve the overall outcome. Current problems faced in different areas were discussed and possible remedial measures were identified. The ultimate aim would be to achieve results comparable to the West.

Recommendations*:* Early recognition, prompt evaluation and algorithm-based management will improve outcome in neonatal cholestasis. Inclusion of stool/urine color charts in well baby cards and sensitizing pediatricians about differentiating conjugated from the more common unconjugated hyperbilirubinemia are possible effective steps. Considering the need for specific expertise and the poor outcome in sub-optimally managed cases, referral to regional centers is warranted.

Keywords: *Cholestatic jaundice, Neonate, Practice guidelines.*

Neonatal cholestasis (NC) is being increasingly recognized as an important cause of chronic liver disease in infants and young children. The etiology and management of cholestasis has changed significantly since the consensus statement last published in 2000 [1]. Three objectives were identified at the previous meeting. First, age at which infants are referred to tertiary care centers is very late for effective evaluation and management and steps need to be taken to address this problem. Second, tertiary centers with pediatric gastroenterology units should follow a uniform protocol of evaluation, and third, the investigation facilities at some centers need to be strengthened, so that a more precise final diagnosis, particularly metabolic disorders, can be arrived at.

A number of steps including a public campaign on 'Yellow alert' and educational programs at pediatric meetings were since held to address the key issues [2,3]. The algorithm put in place in 2001 was followed at almost all major centers, until newer advances were reported. Laboratories in many private and other medical centers are now able to do newer tests for precise diagnosis. This meeting was held to discuss the impact of those programs and to make appropriate changes in the management protocol in the light of recent advances in the subject.

DEFINITION

Neonatal cholestasis is defined as conjugated hyperbilirubinemia occurring in the newborn as a consequence of diminished bile flow. Conjugated hyperbilirubinemia in a neonate is defined as a serum direct/conjugated bilirubin concentration greater than 1.0 mg/dL if the total serum bilirubin (TSB) is <5.0 mg/dL or greater than 20 percent of TSB if the TSB is >5.0 mg/dL [4]. It is important to note that the diazo method of estimating bilirubin, that is still practiced in many Indian centers, tends to overestimate the direct fraction at lower bilirubin levels. The group however felt that the above mentioned definition has to be retained since it is an internationally accepted one.

Conjugated hyperbilirubinemia at any age in a newborn is pathological and requires evaluation. Any newborn with jaundice and dark yellow urine staining the diaper with or without pale stools should be strongly suspected to have NC. Such babies must be referred to an appropriate center for further investigations and treatment at the earliest [1]. Sick newborns and younger infants with deranged liver function tests, particularly uncorrected coagulopathy, require urgent referral to rule out infective or metabolic causes of NC.

ETIOLOGY

NC affects 1 in 2500 infants in the West [4,5]. In India it constitutes 19% to 33% of all chronic liver diseases in children reporting to tertiary care hospitals [1,6-8]. ***Table* I** summarizes the etiologic profile of NC in India. Hepatocellular causes constitute 45% to 69% while obstructive causes account for 19% to 55% of all cases [1,6-12].

While 20 to 30% of cases of NC were idiopathic in earlier studies, [1,6,7,9], recent reports documented this proportion to be lower [2,8,13-18]. The group felt that this emphasizes the need for more exhaustive work up than was recommended earlier. A recent publication with exhaustive workup has shown that Pi-Z and Pi-S alleles responsible for alpha-1 antitrypsin deficiency may be rare in our population [7].

CLINICAL PRESENTATION

Jaundice in newborns is most commonly physiological or due to ABO/Rh hemolytic incompatibility. However, if jaundice is associated with dark urine and/or pale stools, it is suggestive of cholestasis. The sensitivity, specificity, and positive predictive value of pale stools for the detection of biliary atresia (BA) before 60 days as determined by a color-coded stool chart was noted to be 89.7%, 99.9% and 28.6%, respectively [19]. Although cholestasis is known to occur in babies with early onset sepsis [14]. Yet simultaneous screening should be done for metabolic causes. Galactosemia, a treatable cause, may be present even in babies with culture proven sepsis. Babies with tyrosinemia, herpes infection and congenital hemochromatosis may present in a sick state early in life, and their recognition and treatment needs to be incorporated [20]. Non-normalization of liver function tests (LFTs) even after treatment with appropriate antibiotics is a pointer towards an underlying metabolic cause for sepsis [14].

TABLE I ETIOLOGIC PROFILE OF NEONATAL CHOLESTASIS IN INDIA

Etiologic Factor	*N-1008*[*] *(%)*	*N-420*[#] *(%)*
Obstructive causes		
Biliary atresia	34	30
Choledochal cysts	4	5
Hepatocellular causes		
Infections	17	18
Metabolic causes	4	12
Miscellaneous	2	3
Unknown etiology	30	31
Ductal paucity	3	1
Undifferentiated	6	1.2

[*]*Based on cumulative data from eight tertiary care centers [1];* [#]*Data from the largest single series (7).*

Yachha, *et al.* showed that the age of onset of jaundice in BA was 3-12 days and that of hepatocellular causes was 16-24 days [2]. However, the mean age of presentation to a tertiary care center was 2.8–3.9 months compared to the desired age of evaluation, that is 4-6 weeks [2,3,15]. Babies with BA appear well and have normal growth and development in spite of their jaundice, and this leads to parents and physicians underestimating the seriousness of the problem [3]. Many health care professionals also have a misconception that all well babies with icterus have physiological jaundice (which is unconjugated and associated with normal urine color). The group felt that it was a matter of concern that in India the average age of presentation to tertiary care centers has shown little change in the last decade. The group felt that there is a need for creating more awareness among pediatricians and obstetricians on NC and this can be achieved through continuing medical education (CME) programs with the speakers giving the same message by highlighting the recommendations of this consensus statement. Enlarging the scope of the 'yellow alert' to include the whole country through visual and print media would also be beneficial. The Group recommended urine and stool color assessment (minimum 3 stool samples) by the mother and physician in a stool color card incorporated in all well baby cards (Indian Academy of Pediatrics and the Government of India cards). The group also felt that the Taiwanese experience with stool color cards (subsequently replicated in other countries) should be possible in India as well [21].

Persistent cholestasis from any cause leads to liver damage and cirrhosis. Therefore, determining the specific etiology (medical or surgical) at the earliest is critical. Also, the outcome of Kasai portoenterostomy (PE) is directly related to the age of surgery and the

expertise of the treating unit. PE when performed earlier than 60 days of age established adequate bile flow in 64.7% of patients compared with 31.8% when performed later [22,23]. Improved outcome is also noted in centers with a higher case load [24]. In the United Kingdom, a center performing >5 Kasai PE per year, reported significantly better outcome [25]. Hence, babies suspected to have BA require early referral to an appropriate center with expertise in performing PE.

INVESTIGATIONS

Most centers have been following the protocol that was outlined in the earlier consensus statement. However in the light of recent publications and better laboratory support, modifications are required in the evaluation and management protocol. The group felt that laboratory facilities and histopathology support has improved tremendously in the last decade and hence better work up is now possible in many centers. The initial evaluation of an infant with NC includes a complete liver function test (LFT), thyroid function test, and a sepsis screen followed by specific radiological and histopathological tests **(*Fig*. 1)**. The principal diagnostic concerns are to differentiate hepatocellular diseases from anatomical disorders, and diseases that are managed medically from those requiring surgical intervention. The most important initial investigation is to establish cholestasis by measuring serum bilirubin (total and differential) levels. Severity of liver dysfunction can be measured by estimating the prothrombin time or international normalized ratio (INR) and serum albumin. No single laboratory or imaging test exists which differentiates biliary obstruction from other causes of NC reliably in all cases. The serum transaminases are sensitive indicators of hepatocellular injury, but lack specificity and prognostic value. High alkaline phosphatase levels can be seen in biliary obstruction, but has very low specificity. Gamma-glutamyl transpeptidase (GGTP) is a marker of biliary obstruction and is elevated in most cholestatic disorders; paradoxically low or normal levels are found in patients with progressive familial intrahepatic cholestasis (PFIC) and disorders of bile acid synthesis [26].

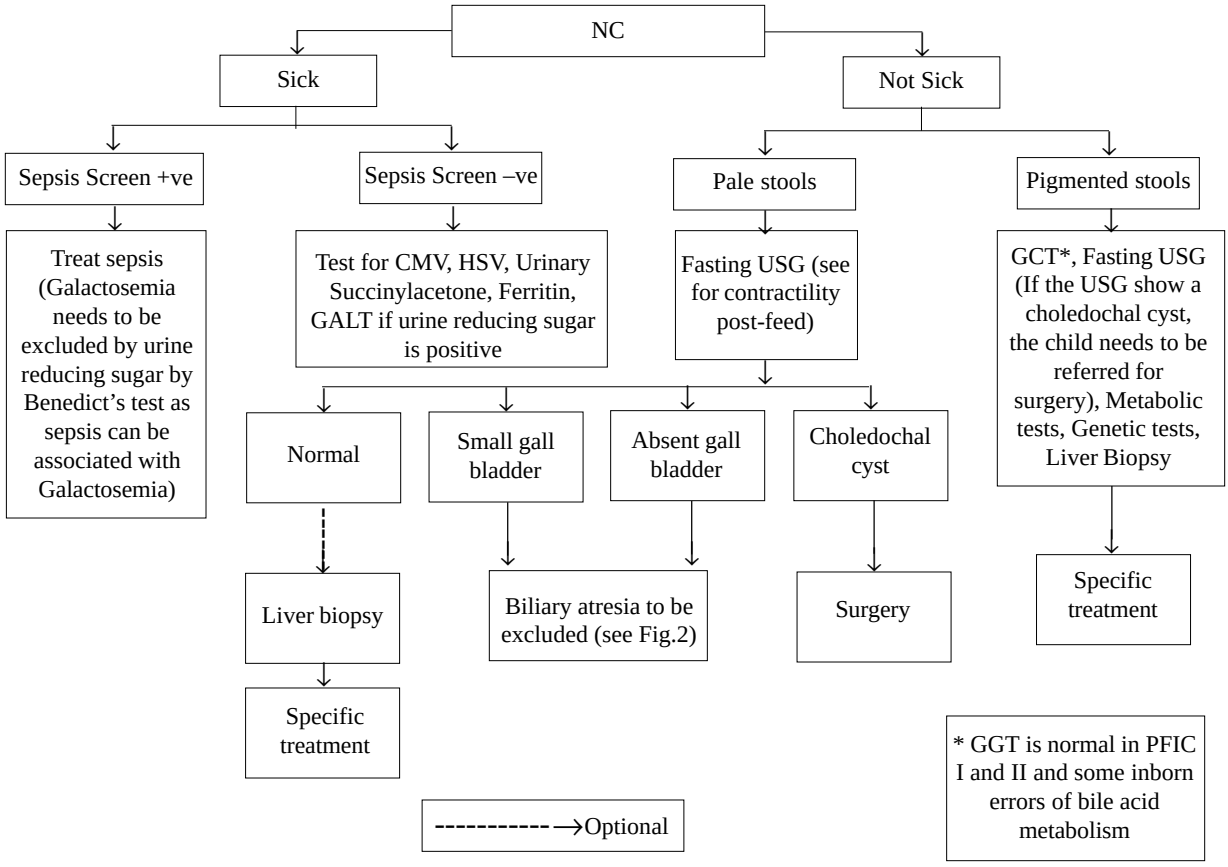

FIG. 1 *Diagnostic algorithm for management of neonatal cholestasis (Part 1).*

Abdominal ultrasonography may provide findings suggestive of BA and can also be used to confirm the existence of other surgically treatable conditions like choledochal cyst, inspissated bile plug syndrome and choledocholithiasis. Abdominal ultrasonography findings described in BA include the triangular cord sign [27], abnormal gallbladder morphology (not visualized or length <1.9 cm or lack of smooth/complete echogenic mucosal lining with an indistinct wall or irregular/lobular contour) [19], no contraction of the gallbladder after oral feeding and non-visualized common bile duct (CBD). A distended gall bladder, however, does not rule out a proximal BA with a distal patent bile duct and mucus filled gallbladder. It is recommended that ultrasound should be done after 4 hours of fasting.

Hepatobiliary-imino-di-acetic acid (HIDA) scan has limited role in evaluation of NC especially if the baby has clearly documented pale or pigmented stools. The time required (5-7 days) for priming before the scan, especially in patients who are referred late, is a limitation. The group felt that good-quality HIDA scan may not be available everywhere in our country, and therefore, delaying the liver biopsy for it is not justified. Performing a HIDA scan is optional and one may go for a liver biopsy straightaway **(*Fig.* 2)**. HIDA is, however, useful in the diagnosis of the uncommon causes like spontaneous perforation of the bile duct [28]. Intra-operative cholangiogram (IOC) remains the gold standard for diagnosis of BA.

Liver biopsy is an essential investigation in the evaluation of NC. Early recognition of BA by liver biopsy can avoid unnecessary laparotomy (5). The characteristic histopathology features of BA are bile duct proliferation, bile plugs in ducts, fibrosis and lymphocytic infiltrates in the portal tracts. The reported sensitivity, specificity and accuracy of liver biopsy in the diagnosis of BA are 89-99%, 82-98% and 60-95%, respectively [16]. Percutaneous liver biopsy in early infancy under local anesthesia and sedation is a safe procedure, if performed by competent physicians [29]. The group opined that the biopsy must be interpreted by an experienced pathologist in conjunction with the clinical profile and results of the other investigations. In cases of doubt, a second opinion should be sought.

In galactosemia, urine is positive for non-glucose reducing substances while the infant is on lactose feeds. *E. coli* sepsis in the presence of liver cell dysfunction is very characteristic of galactosemia. Assay of Galactose-1 phosphate uridyl transferase (GALT) enzyme is used for confirmation. Mutational analysis of the GALT gene from Indian subjects has revealed heterogeneity in the structure of the gene and the presence of novel mutations [30,31]. Hereditary fructose intolerance (HFI) is not an uncommon cause of neonatal cholestasis in our country as there are many states where sugar water continues to be given to newborns until lactation is fully established. It should be considered in clinical settings where sucrose or fruit juices have been given to babies. Assay of aldolase B enzyme in liver biopsy sample confirms HFI. Fructose challenge test can make the child very ill and is now obsolete. Plasma tyrosine levels are unreliable in the diagnosis of tyrosinemia. Measurement of urinary succinylacetone and succinyl acetoacetate or assay of the FAH gene is diagnostic [32]. Among the congenital infections, cytomegalovirus (CMV) is most commonly implicated. Serum IgM level is unreliable in diagnosis and should not be used. Assay of pp65 antigen and CMV polymerase chain reaction (PCR) are more specific and reliable, if the biochemical tests and histology are consistent with the diagnosis. Markedly raised serum ferritin and uncorrected coagulopathy are suggestive of hemochromatosis that may be confirmed by a buccal mucosal biopsy.

A two part diagnostic algorithm to help in the management of NC is given in ***Fig*.1** and ***Fig*. 2**.

TREATMENT

General Medical Management

Most infants with NC are underweight and will need nutritional support. The goal is to provide adequate calories to compensate for steatorrhea and to prevent/ treat malnutrition. The calorie requirement is approximately 125% of the recommended dietary allowance (RDA) based on ideal body weight [33]. In breastfed infants, breastfeeding should be encouraged and medium-chain triglyceride (MCT) oil should be administered in a dose of 1-2 mL/kg/d in 2-4 divided doses in expressed breast milk [34]. In older infants, a milk-cereal-mix fortified with MCT is preferred. Adding puffed rice powder and MCT to milk can make feeds energy-dense. Essential fatty acids should constitute 2-3% of the energy provided. Vegetable protein at 2-3 g/kg/ d is recommended [34].

Infants with cholestasis require supplementation with fat-soluble vitamins administered orally as water-soluble preparations. Suggested daily vitamin and mineral supplementation are given in ***Table* II**. In treatment of vitamin deficiencies, standard deficiency protocols should be followed. 1,25 dihydroxy Vitamin D3 (0.05-0.2 ug/kg/d) is recommended in the presence of significant bone changes or patients having severe cholestasis [34]. Vitamin K is administered at a dose of 5 mg

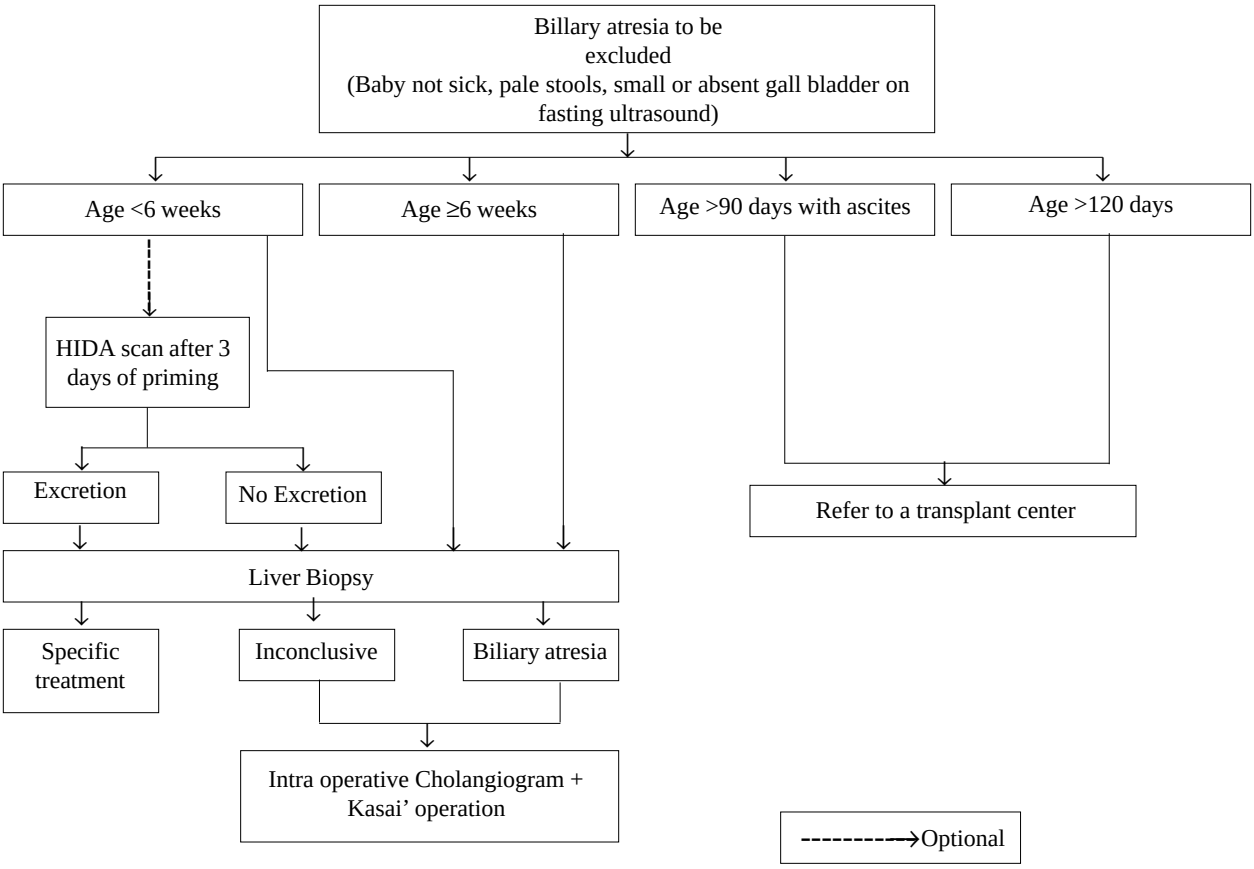

FIG. 2 *Diagnostic algorithm to help in the management of neonatal cholestasis (Part 2).*

intramuscular, subcutaneously or intravenously, at diagnosis to correct the coagulopathy. If the INR is markedly prolonged, intramuscular injections should be avoided. Vitamin supplementation should be continued till 3 months after resolution of jaundice [35].

Specific treatment

Special infant formula and diets are recommended for children with specific diagnosis (galactosemia, fructosemia and tyrosinemia). However these formulae are currently not available in India. The group feels that steps must be taken to make them available at the earliest. Treatment with nitisinone (1 mg/kg/d) in addition to dietary restriction leads to rapid reduction of toxic metabolites in tyrosinemia. Specific therapy is recommended for patients with CMV (associated neurological involvement), herpes and toxoplasmosis related cholestasis. There is no role for steroids in idiopathic neonatal hepatitis.

In infants with pruritus due to severe cholestasis, the group recommended, in the following order: Ursodeoxycholic acid (UDCA) (20 mg/kg/d), rifampicin (5-10 mg/kg/d), and phenobarbitone (5–10 mg/kg/d). Symptom chart should be made for pruritus. Depending on severity and response to previous agent, add-on drug can be considered. Appropriate antibiotics depending on the site of infection and culture sensitivity reports need to be administered in patients with bacterial sepsis.

Kasai's PE consists of removal of the atretic extra-hepatic tissue and a Roux-en-Y jejunal loop anastomosis to the hepatic hilum. PE may be considered successful if serum bilirubin normalizes after surgery. In general, over half the patients normalize their bilirubin after Kasai's PE if performed within six months [36]. About 20% of all patients undergoing Kasai's PE during infancy survive into adulthood with their native liver [36,37]. In children with progressive familial intrahepatic cholestasis (PFIC) without decompensated cirrhosis, external and internal biliary diversion has been shown to be of benefit [38]. Surgery gives excellent results for choledochal cysts and should be performed as soon as the diagnosis is made. The recent consensus statement of the Pediatric Gastroenterology chapter on Acute liver failure gives more details on the management of liver failure in NC [39].

TABLE II SUGGESTED DAILY VITAMIN AND MINERAL REQUIREMENTS IN INFANTS WITH CHOLESTASIS

	Route	*Dose**
Vitamin A[#]	Oral	5000-25,000 IU/d
Vitamin D	Oral	400-1200 IU/d
Vitamin E	Oral	50-400 IU/d or 15-25 IU/ kg/d of TPGS form if available
Vitamin K[$]	Oral	2.5 twice/week to 5 mg/d
	Parenteral	2-5 mg IM, SC or IV 4 weekly
Water soluble vitamins	Oral	1-2 times the RDA
Calcium[**]	Oral	20-100 mg/kg/d
Phosphorus	Oral	25-50 mg/kg/d
Zinc	Oral	1 mg/kg/d
Magnesium	Oral	1-2 mEq/kg/d
	Intravenous	0.3-0.5 mEq/ kg over 3 hours of 50% solution
Elemental iron	Oral	5-6 mg/kg/d

Adapted from Ref. 39

**Doses are provided as a guide only and will need to be adjusted based on response and levels of the vitamins. [#]Careful monitoring required as Vitamin A itself is hepatotoxic; [$]Vitamin K1 preparation preferred, as it is safe for G6PD deficient individuals; [**]Calcium should always be supplemented along with Vitamin D.*

Liver transplantation

Liver Transplantation, the standard therapy for decompensated cirrhosis due to any cause, is now well established in India as well [40]. Any baby, who has had Kasai's PE and the bilirubin remains >6 mg/dL, three months after surgery, should be referred to a transplant center. Babies with BA who present with decompensated cirrhosis (low albumin, prolonged INR, ascites) are not likely to improve with a Kasai PE and should be referred for liver transplantation. Of the 355 transplants in children that have been performed in India till 2012, 30% have been for BA [41]. Living related liver transplantation (the vast majority of liver transplants in India are living related), performed at experienced centers, is associated with favorable outcomes, with 5- and 10-year survival rates of 98% and 90%, respectively [42-44].

CONCLUSIONS AND RECOMMENDATIONS

- NC constitutes almost one-third of children with chronic liver disease in major hospitals in India. BA, NH and metabolic causes are the most important causes in India.
- Early identification of the cause is essential for a favorable outcome. This requires specific biochemical tests, imaging studies and interpretation of histopathology by experienced personnel and is now possible in major centers all over India.
- The overall outcome in India is far from satisfactory, due to late referral. The mean age at presentation in tertiary care centers is still over 3 months compared to recommended age of less than 60 days.
- To ensure early referral, there is an urgent need to sensitize pediatricians, obstetricians and other primary-care physicians on the need for early evaluation. 'Yellow alert' should be extended to an All-India level and the stool color card should be incorporated in the well-baby cards of IAP and the Government of India.
- Metabolic diseases (*e.g.* galactosemia, fructosemia, hemochromatosis, tyrosinemia) and inherited diseases like PFIC are increasingly being diagnosed in tertiary centers. Establishment of regional referral labs will enable greater diagnosis of causes of NC.
- Ultrasound, isotope scan and liver biopsy interpretation in experienced hands are effective in ruling out surgical causes in a majority of cases. If BA cannot be ruled out with certainty, an experienced surgeon should perform a laparotomy andintra-operative cholangiography.
- Malnutrition adversely affects the outcome in infants with cholestasis. Nutritional support and vitamin/ mineral supplementation is recommended in all babies with NC. Special formulae may have a role in select cases.
- When NC leads to liver failure, LT should be offered. Success rates in India are comparable to those in the West.

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Competing interests: None stated

APPENDIX

List of Invited Participants

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Chowdhary*, Sumathi B., Sutapa Ganguly, Ujjal Poddar*, VS Sankaranarayanan, Veena Malhotra, Vibhor Borkar, Vidyut Bhatia (VB), Vishnu Biradar, Yogesh Waikar (YW)

**Contributed but could not attend the Round Table Conference on 8th December 2012.*

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