Indian Academy of Pediatrics (IAP)

STANDARD TREATMENT GUIDELINES 2022

Neonatal Cholestasis

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Neonatal Cholestasis

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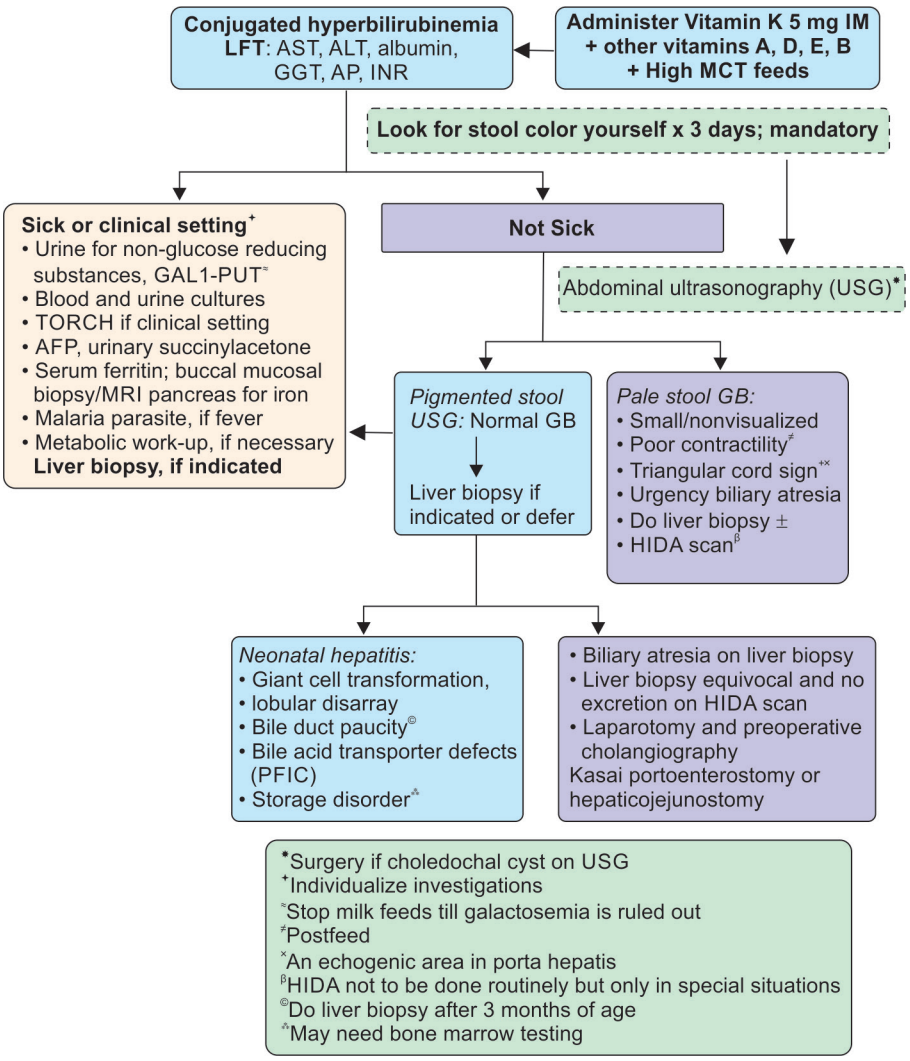
Definition

Neonatal cholestasis (NC) is defined as conjugated bilirubin >1 mg/dL (if total <5 mg/dL) or >20% of total serum bilirubin (if total >5 mg/dL) with passage of dark-colored urine staining the diapers with or without acholic stools.

Causes of Neonatal Cholestasis in India

Disease groups (N = 1,008)	***Causes in each subgroup***
A. *Hepatocellular 53% (n = 533)*	
Neonatal hepatitis 47% (n = 468)	☑ Idiopathic giant cell hepatitis ☑ TORCH infections ☑ Sepsis ☑ Other causes such as malaria and urinary tract infection (UTI)
Metabolic 4% (n = 43)	Galactosemia, alpha-1-antitrypsin (α1AT) deficiency (suspected), total parental nutrition (TPN) related, tyrosinemia, storage disorders, and hemochromatosis
Other causes 2% (n = 22)	Inspissated bile plug syndrome, progressive familial intrahepatic cholestasis (PFIC), hypothyroidism, associated Down's syndrome; and rare causes such as polycystic disease, post-intestinal surgery, and immunodeficiency
B. *Obstructive 38% (n = 383)*	Biliary atresia and choledochal cyst
C. *Ductal paucity 3% (n = 29)*	Syndromic variety (Alagille syndrome and nonsyndromic variety)
D. *Unknown 6%*	
Other causes of NC not listed above may be due to other conditions such as bile acid synthetic disorders, Coombs-positive giant cell hepatitis, and neonatal sclerosing cholangitis. A number of new subtypes are being diagnosed now in India like bile acid transporter defects formerly called PFIC. With newer disorders the proportion of idiopathic group of NC is now shrinking.	

Approach to a Case of Neonatal Cholestasis



(AFP: alpha-fetoprotein; ALT: alanine transaminase; AP: alkaline phosphatase; AST: aspartate transaminase; GAL1-PUT: galactose-1-phosphate uridyltransferase; GB: gallbladder; GGT: gamma-glutamyl transferase; HIDA: hepatobiliary iminodiacetic acid; INR: international normalized ratio; LFT: liver function test; MCT: medium chain triglycerides; PFIC: progressive familial intrahepatic cholestasis)

Disease entity	Specific investigations		Specific treatment
	Screening	Confirmatory	
Biliary atresia (BA)	Pale-colored stool, high GGT, USG: GB rudimentary/poor contractility, triangular cord sign+; liver biopsy features of BA	Peroperative cholangiogram	☑ *Surgical:* Portoenterostomy in the large majority of cases Or ☑ Hepaticojejunostomy in a few with patent confluence at porta
Galactosemia	Urine for nonglucose reducing substances +	Galactose-1-phosphate uridyltransferase (GAL1-PUT)	Lactose-free diet
Tyrosinemia	High AFP	Urinary succinylacetone present (being highly volatile substance sample should be quickly analysis)	Drug treatment with NTBC [2-(2-nitro-4-trifluoromethylbenzoyl)-1, 3-cyclohexanedione] and restricted tyrosine and phenylalanine diet Alternatively liver transplantation
Gestational alloimmune liver disease (earlier named as neonatal hemochromatosis)	High serum ferritin median 2,448 (415–100,000) µg/L	*Lip biopsy (submucosal gland):* Iron deposition on staining Or MRI pancreas for iron deposition	High dose of intravenous immunoglobulin ± exchange blood transfusions. If no response, then liver transplantation
Bile acid transporter defects (PFIC types 1-VI; types I-III being common)	☑ *GGT:* Normal/low, high ☑ Liver biopsy features	Genetic evaluation (clinical exome sequencing)	Medical treatment for pruritus. May need surgical biliary diversion to control pruritus. Liver transplantation, if indicated
Alagille syndrome	High GGT; high triglycerides; eye, cardiac, and skeletal specified defects; paucity of bile ducts on liver biopsy	Genetic evaluation JAG 1 or NOTCH 2 mutation	Same as that of bile acid transporter defects with some exceptions in managing disease complications

Supportive Management in Neonatal Cholestasis

Drug/supplementation	*Dose*	*Side effects/comment*
Vitamin K	2.5 mg twice/week to 5 mg/day oral Or IV/IM: 2–5 mg/month	None *(To be given if coagulopathy is present or till conjugated jaundice is existing)*
Vitamin D (cholecalciferol)	Oral 2,500–4,000 IU/day Or One sachet (60,000 IU) per month	Hypercalcemia, nephrocalcinosis *(To be given if coagulopathy is present or till conjugated jaundice is existing). May monitor vitamin D levels every 3 monthly and treat accordingly).*
Vitamin A	Oral 5,000–25,000 IU/day	Hepatotoxicity, hypercalcemia Pseudotumor cerebri if higher dose is used. Avoid hypervitaminosis as it can enhance liver fibrosis
Vitamin E	Oral 50–400 IU/day	Potentiation of vitamin K deficiency coagulopathy, diarrhea
Water-soluble vitamins	Twice the recommended daily allowances	None
Calcium supplementation	Oral 25–100 mg/kg/day	
Medium chain triglycerides (MCT)	15–20% of calories	Oral supplementation in the form of oil/powder/formula feeds containing desired MCT content
Pruritus (oral drugs)▫		
Ursodeoxycholic acid	10–20 mg/kg/day	Diarrhea, hepatotoxicity
Rifampicin	10 mg/kg/day	Hepatotoxicity, drug interactions
Phenobarbitone	3–10 mg/kg/day	Sedative effect, behavioral changes
Cholestyramine	0.25–0.5 g/kg/day	Constipation, steatorrhea, hyperchloremic metabolic acidosis

Note: Vitamins to be administered in all cases of NC irrespective of etiology. Fat- and water-soluble vitamins to be given till conjugated jaundice is present otherwise when indicated depending upon the disease status.

▫ Recently newer drugs have been tried as ileal (intestinal) bile acid transport inhibitors for treating cholestatic liver disease

Further Reading

- ☑ Bhatia V, Bavdekar A, Matthai J, Waikar Y, Sibal A. Management of Neonatal Cholestasis: Consensus Statement of the Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics. Indian Pediatr. 2014;51:203-10.
- ☑ Feldman AG, Sokol RJ. Recent developments in diagnostics and treatment of neonatal cholestasis. Semin Pediatr Surg. 2020;29:150945.
- ☑ Indian Academy of Pediatrics. Consensus Report on Neonatal Cholestasis Syndrome. Pediatric Gastroenterology Subspecialty Chapter of Indian Academy of Pediatrics Document. Indian Pediatr. 2000;37:845-51.