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Towards a Precise Definition of Neonatal Cholestasis Diagnosis

Mohammad Mahmod Al Khubbi[1] and Mohamed Abouseif Badawi[2]*

[1]Registrar Pediatric and Neonatologist, NICU, AL Qassimi Women's and Children Hospital (AQWCH), Emirates health Services (EHS), Sharjah, United Arab Emirates

[2]Consultant Neonatology, NICU, AL Qassimi Women's and Children Hospital (AQWCH), Emirates Health Services (EHS), Sharjah, United Arab Emirates

***Corresponding Author:** Mohamed Abouseif Badawi, Adjunct Clinical Assistant Professor of Pediatric and Neonatology, College of Medicine, University of Sharjah, M.B., B. Ch., M.Sc. Pediatrics, MRCPCH (UK), FRCPCH (UK), CABP (Certified Arab Board of Paediatrics), Neonatal perinatal fellowship (ABP), ABP Program Mentor, ABP Neonatal fellowship program Mentor, United Arab Emirates.

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Neonatal jaundice, characterized by yellowish discoloration of the skin and eyes, is commonly observed in newborns during the first two weeks of life. While up to 15% of breastfed infants may develop jaundice, most cases are due to elevated levels of indirect (unconjugated) bilirubin. However, jaundice can also be linked to increased conjugated bilirubin, which may signal underlying liver, metabolic or diversities of other diseases.

In any term or preterm neonates who continue to have jaundice after 2 weeks or 3 weeks of age respectively or those with additional symptoms such as pale stools, diarrhea, poor weight gain, hepatomegaly or splenomegaly, it is important to measure the serum bilirubin levels and separate them into direct (conjugated) and indirect (unconjugated) components.

Cholestasis, results from impaired bile flow or excretion with accumulation of bile substances in the blood and extrahepatic tissues. It is clinically identified when the direct bilirubin (DB) level exceeds 1 mg/dL (17.1 mmol/L) when a total bilirubin level less than 5 mg/dL (85.5 mmol/L), or when direct bilirubin more than 15 - 20% of the total bilirubin when the total exceeds 5 mg/dL (85.5 mmol/L). Recent studies indicate that in the first five days after birth, cholestasis should be suspected if the conjugated bilirubin level is greater than 0.3 to 0.4 mg/dL (5.1 - 6.8 mmol/L; or above the upper limit of normal in newborns for the laboratory) or greater than 10% of the total bilirubin.

Cholestasis is never considered normal and requires immediate evaluation to identify the underlying cause. The most known causes of neonatal cholestasis include biliary atresia (BA) (25% - 40%), genetic and metabolic conditions such as alpha-1 antitrypsin (A1AT) deficiency (10% - 20%), Alagille syndrome (ALGS) (2% - 14%), cystic fibrosis (CF), progressive familial intrahepatic cholestasis (PFIC), and hypopituitarism (5%). Other potential causes include inspissated bile syndrome, idiopathic neonatal hepatitis (INH)/transient neonatal cholestasis (TNC) and parenteral nutrition-associated cholestasis (PNAC), especially in preterm infants or those with intestinal failure.

Treatable conditions, such as galactosemia, tyrosinemia, bacterial and viral sepsis, choledochal cyst and biliary atresia (BA), can be managed with medical or surgical interventions that may help prevent liver failure or serious extrahepatic complications.

Regardless of the cause, infants with cholestasis should receive optimal nutritional support, fat-soluble vitamin supplementation, and care to manage or prevent complications associated with liver disease, such as cholangitis, bleeding diathesis, failure to thrive, portal hypertension, and ascites.

Neonatal cholestasis (NC) definition:

- DB > 1 mg/dL ([17.1 mmol/L] when the total bilirubin is < 5 mg/dL [85.5 mmol/L].
- DB > 15 - 20% when the total bilirubin is > 5 mg/dL [85.5 mmol/L].
- DB > 0.3 - 0.4 mg/dL (5.1 - 6.8 mmol/L) or >10% of the total bilirubin within the first 5 days after birth.

Table

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