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Etiologies and Initial Evaluation of Neonatal Jaundice

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Abstract

Neonatal jaundice is seen in up to 60% of full-term infants and 80% of preterm infants during the first week of life. While it is often considered as a single clinical entity, neonatal jaundice is a physical finding associated with many possible etiologies. Jaundice is observed when the pigment bilirubin accumulates in the skin, sclera and other tissues. The importance of correctly identifying the etiology of neonatal jaundice lies in the necessity of intervening early to avoid the devastating sequelae of prolonged hyperbilirubinemia, namely bilirubin-induced neurological dysfunction (BIND), formerly kernicteruskernicterus. This manuscript provides a framework for thinking about the etiologies of neonatal jaundice with respect to type of hyperbilirubinemia (direct *vs.* indirect) and age of the newborn.

Keywords: Jaundice; Kernicterus; Bilirubin; Neonatal

Etiologies of neonatal jaundice

Physiologic neonatal jaundice encompasses three major mechanisms [1-3] of hyperbilirubinemia in the newborn: reduced conjugation, increased enterohepatic circulation, and increased production of bilirubin. Almost all newborns have decreased conjugation and excretion processes at birth [2], due to the low activity of UDP-glucuronosyltransferase (UGT) in hepatocytes and a paucity of intestinal flora that convert bilirubin to urobilinogen, resulting in increased enterohepatic circulation. Moreover, fetal red blood cells turn over more frequently than do adult red blood cells [4-6], resulting in a shorter life span and more heme degradation in neonates. These are the bases of physiologic jaundice in the newborn, which can be successfully treated in most cases with phototherapy or exchange transfusion [3,4].

Figure 1 represents a summary of the etiologies and initial work-up discussed below. Pathologic indirect hyperbilirubinemia on days 1-3 of life usually results from hemolysis. Early causes of hemolysis include blood group incompatibilities like Rh and Kell. On days of life 3-7, hemolysis may result from ABO blood group incompatibilities. Hemolysis from blood group incompatibility arises from maternal immunoglobulins against fetal red cell antigens. The classic teaching is that mothers exposed to incompatible red cell antigens in prior pregnancies develop IgG antibodies against unfamiliar blood groups; these immunoglobulins then cross the placenta in subsequent pregnancies and bind fetal red cells, leading to their destruction by the spleen. Mothers may also be exposed to unfamiliar red cell antigens from blood transfusions earlier in life. Hemolysis from blood group incompatibility is seen with ABO incompatibility, Rh incompatibility, and incompatibility of other blood groups like Kell, Duffy and Lewis.

Other causes of hemolysis presenting at days of life 3-7 are glucose-6-phosphate dehydrogenase (G6PD) deficiency [7,8], sickle cell anemia, the thalassemias, hereditary spherocytosis, and sepsis [9,10] G6PD deficiency results from lower than normal concentrations of the enzyme glucose-6-phosphate dehydrogenase; its absence leaves red cells unable to generate sufficient amounts of glutathione (a major cellular antioxidant) and thus vulnerable to oxidative damage that results in hemolysis. Hemoglobinopathies, like sickle cell anemia and alpha thalassemia, are genetic aberrations that yield structurally abnormal globin chains or low levels of specific globin chains; red cells are deformed from the polymerization and/or precipitation of abnormal hemoglobin tetramers, ultimately resulting in hemolysis. Defects in structural proteins on the red cell membrane (e.g. spectrin, ankyrin, band 3 and protein 4.2) give rise to hereditary spherocytosis; the spherocytic red cells are prematurely removed by the spleen, resulting in hemolysis and indirect hyperbilirubinemia.

Inability to substantially upregulate glucuronidation as in Gilbert's syndrome, and Crigler-Najjar (extremely rare), also presents at 3-7 days of life with indirect hyperbilirubinemia [2], as does breastfeeding failure jaundice. In Crigler-Najjar syndrome type 1, there is complete absence of UDP glucuronosyltransferase activity, and the result is bilirubin encephalopathy in the first days to months of life [11]. Neonates with Gilbert's syndrome have mildly decreased activity of UDP-glucuronosyltransferase,4 as well as deficient hepatic uptake of unconjugated bilirubin, both of which lead to indirect hyperbilirubinemia. Of note, Gilbert's syndrome coupled with glucose-6-phosphate dehydrogenase deficiency compounds the likelihood of severe indirect hyperbilirubinemia [2,12,13]. Breastfeeding failure jaundice arises from lactation failure resulting in reduced oral intake for the neonate. Reduced feeding results in slower bilirubin elimination and increased enterohepatic circulation, resulting in indirect hyperbilirubinemia.

With the exception of breast milk jaundice (which peaks at 2 weeks), neonatal jaundice beyond the first 14 days of life is very often a result of direct hyperbilirubinemia [2,3], for which there exist two classes of etiologies: hepatic and post-hepatic causes. The hepatic causes of direct hyperbilirubinemia encompass metabolic and infectious entities including: Dubin-Johnson and Rotor syndromes, cystic fibrosis, alpha 1-antitrypsin deficiency, galactosemia, ToRCHeS infections, viral hepatitis, and neonatal sepsis. In general, conjugated bilirubin is transported from hepatocytes into the bile canaliculi through the multidrug resistance related protein 2 (MRP2). Mutations in MRP2 are associated with Dubin-Johnson syndrome, resulting in the inability to

excrete conjugated bilirubin into the bile. In contrast, Rotor syndrome results from dysregulation of processes that allow for distal canalicular excretion of conjugated bilirubin when proximal canalicular excretory mechanisms are saturated. Both of these disease processes are inherited defects of conjugated bilirubin excretion. Similarly, in cystic fibrosis impaired CFTR results in thick and tenacious bile that obstructs intrahepatic bile ducts, potentially leading to obstructive jaundice and direct hyperbilirubinemia.

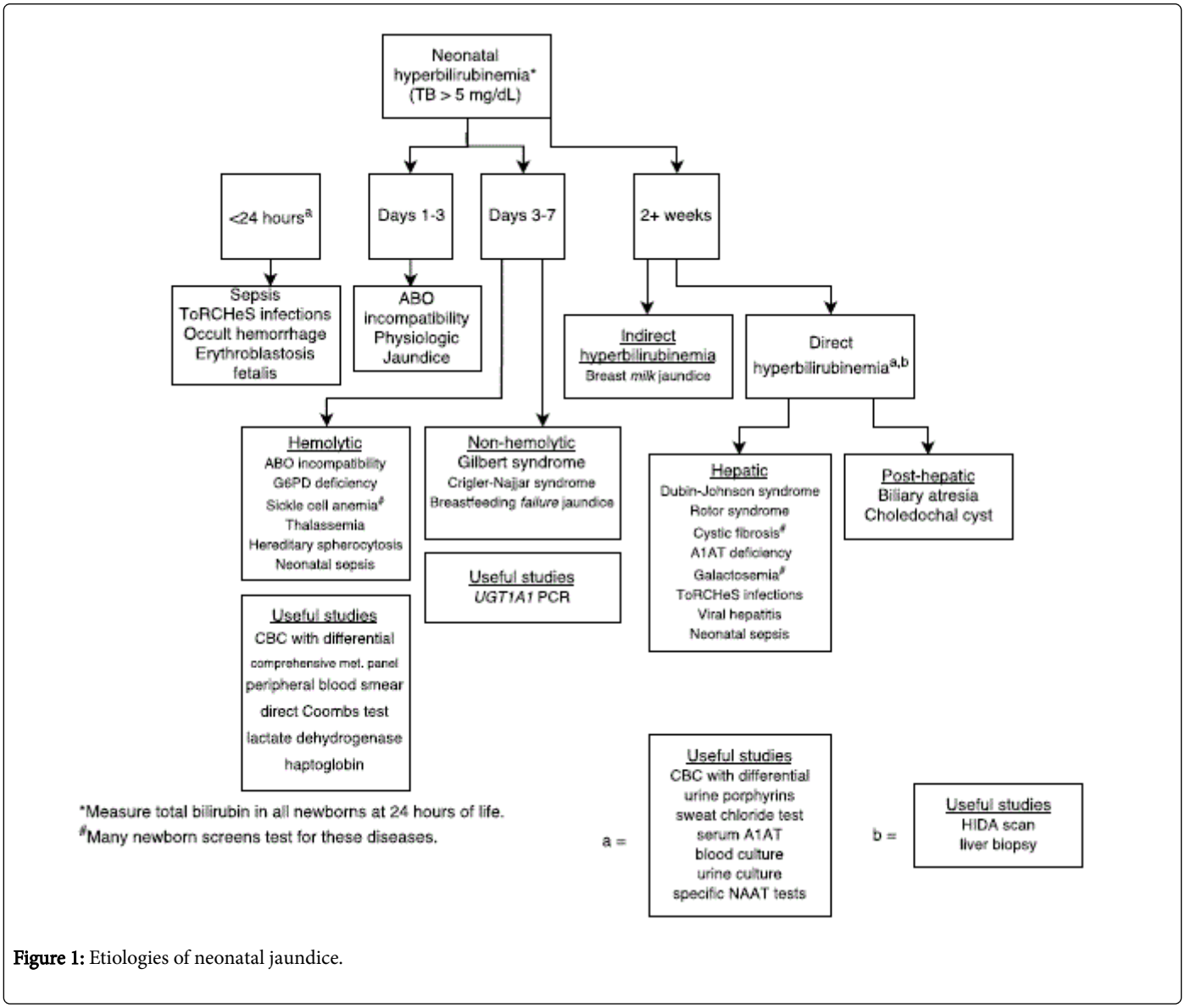

Figure 1: Etiologies of neonatal jaundice.

The most dreaded post-hepatic cause of direct hyperbilirubinemia is biliary atresia, which requires a hepatoportoenterostomy (i.e. Kasai procedure) early in life, and liver transplantation several years later. The cause of congenital biliary atresia is largely unknown. The less concerning cause of post-hepatic direct hyperbilirubinemia is choledochal cyst(s), which may obstruct the flow of bile through the biliary tree, also necessitating surgical correction; however, obstructive jaundice caused by a choledochal cyst is exceptionally rare.

Correctly identifying the underlying cause of neonatal jaundice allows early intervention to avoid the devastating sequelae of prolonged hyperbilirubinemia. High concentrations of bilirubin in the blood eventually reach the basal ganglia5 and other brain structures, resulting in irreversible neurologic impairment, termed BIND (formerly kernicterus). Clinical manifestations of BIND include: poor feeding, lethargy, hypotonia, seizures, hypertonia (late), coma, and death [4].

Initial evaluation of neonatal jaundice

The evaluation and risk stratification of neonates with hyperbilirubinemia is an important first step in the prevention of bilirubin-induced neurologic dysfunction. Although many newborn infants develop a total bilirubin (TB) level that exceeds 1 mg/dL (the upper limit of normal in adults), severe neonatal hyperbilirubinemia is defined as TB>25 mg/dL [14,15]. This level is associated with an increased propensity for bilirubin to cross the blood-brain barrier and bind to brain tissue, leading to devastating neurologic dysfunction, including acute bilirubin encephalopathy (ABE) and BIND. With the

current advances in medical care, there are still many phenomena that may contribute to the development of ABE and kernicterusBIND; they include, but are not limited to, discharge before 48 hours after birth without appropriate follow-up, failure to measure total bilirubin concentrations within 24 hours of birth, failure to recognize risk factors for hyperbilirubinemia, and delayed initiation of phototherapy in infants with elevated total bilirubin [16,17]. Given that many of these causes are preventable, a great deal of investigation and effort has been put forth to establish a systematic approach to infants with jaundice hyperbilirubinemia and reduce the rates of bilirubin-induced sequelae.

The first step in this approach is screen all newborns for hyperbilirubinemia at 24 hours of life. TB can also be measured at the time of regular newborn screening for metabolic disorders without obtaining an additional blood sample. As a result of this ease in practice, universal screening is typically performed in all neonates prior to discharge from the hospital, though the United States Preventive Services Task Force does not recommend it [18-20]. This measurement can then be compared to age-specific percentile-based nomograms to predict the risk of clinically significant hyperbilirubinemia.

Whether or not screening with TB is performed prior to discharge, follow-up is a crucial part of preventing bilirubin-associated pathology. The timing of this follow up is dependent on whether or not the neonate has risk factors for the development of hyperbilirubinemia and the age of the neonate at discharge. Major risk factors for the development of hyperbilirubinemia include jaundice observed within the first 24 hours of life, known hemolytic disease (e.g. G6PD deficiency), gestational age 35-36 weeks, previous sibling who received phototherapy and East Asian race [14]. Infants discharged prior to the peak of TB concentrations (usually 72-96 hours of age) will require follow-up at an earlier time to assess for jaundicehyperbilirubinemia [4,21,22]. In general, the younger the neonate at discharge, the earlier the infant will need follow-up [23,24]. Importantly, if this follow-up cannot be ensured, the neonate's discharge from the hospital should be delayed until the time period during which the highest risk of hyperbilirubinemia has passed. At the follow-up appointment, the infant's interval history since discharge, as well as physical exam, should be used to guide the necessity for additional TB measurements.

References

1. Mishra JP, Mishra J, Padhi RK, Mishra S, Manjareeka M (2014) Hematological profile in neonatal jaundice. J Basic Clin Physiol Pharmacol 25: 225-228.
2. Cohen RS, Wong RJ, Stevenson DK (2010) Understanding neonatal jaundice: a perspective on causation. Pediatr Neonatol 51: 143-148.
3. Weng, Y (2012) Understanding the Pathophysiology of Neonatal Jaundice. J Neonatal Biol 1: 1-2.
4. Dennery PA, Seidman DS, Stevenson DK (2001) Neonatal hyperbilirubinemia. N Engl J Med 344: 581-590.
5. Martich-Kriss V, Kollias SS, Ball WS Jr (1995) MR findings in kernicterus. AJNR Am J Neuroradiol 16: 819-821.
6. Brouillard RP (1974) Measurement of red blood cell life-span. JAMA 230: 1304-1305.
7. MacDonald MG (1995) Hidden risks: early discharge and bilirubin toxicity due to glucose 6-phosphate dehydrogenase deficiency. Pediatrics 96: 734-738.
8. Slusher TM, Vreman HJ, McLaren DW, Lewison LJ, Brown AK, et al. (1995) Glucose-6-phosphate dehydrogenase deficiency and carboxyhemoglobin concentrations associated with bilirubin-related morbitidity and death in Nigerian infants. J Pediatr 126: 102-108.
9. Johnson JD, Angelus P, Aldrich M, Skipper BJ (1986) Exaggerated jaundice in Navajo neonates. The role of bilirubin production. Am J Dis Child 140: 889-890.
10. Fischer AF, Nakamura H, Uetani Y, Vreman HJ, Stevenson DK (1988) Comparison of bilirubin production in Japanese and Caucasian infants. J Pediatr Gastroenterol Nutr 7: 27-29.
11. Green RM and Gollan JL (1997) Crigler-Najjar diease type I: therapeutic approaches to genetic liver diseases into the next century. Gastroenterology 112: 649-651.
12. Kaplan M, Rubaltelli FF, Hammerman C, Vilei MT, Leiter C, et al. (1996) Conjugated bilirubin in neonates with glucose-6-phosphate dehydrogenase deficiency. J Pediatr 128: 695-697.
13. Kaplan M, Renbaum P, Levy-Lahad E, Hammerman C, Lahad A, et al. (1997) Gilbert syndrome and glucose 6-phosphate dehydrogenase deficiency: a dose-dependent genetic interaction crucial to neonatal hyperbilirubinemia. Proc Natl Acad Sci USA 94: 12128-12132.
14. Pediatrics 114: 297-316.
15. Bhutani VK, Johnson L (2009) Kernicterus in the 21st century: frequently asked questions. J Perinatol 29 Suppl 1: S20-24.
16. Johnson LH, Bhutani VK, Brown AK (2002) System-based approach to management of neonatal jaundice and prevention of kernicterus. J Pediatr 140: 396-403.
17. Johnson L, Bhutani VK, Karp K, Sivieri EM, Shapiro SM (2009) Clinical report from the pilot USA Kernicterus Registry (1992 to 2004). J Perinatol 29 Suppl 1: S25-45.
18. Riskin A, Tamir A, Kugelman A, Hemo M, Bader D (2008) Is visual assessment of jaundice reliable as a screening tool to detect significant neonatal hyperbilirubinemia? J Pediatr 152: 782-787, 787.
19. Keren R, Tremont K, Luan X, Cnaan A (2009) Visual assessment of jaundice in term and late preterm infants. Arch Dis Child Fetal Neonatal Ed 94: F317-322.
20. US Preventive Services Task Force (2009)Screening of infants for hyperbilirubinemia to prevent chronic bilirubin encephalopathy: US Preventive Services Task Force recommendation statement. Pediatrics 124: 1172-1173.
21. Brown AK (1962) Bilirubin metabolism with special reference to neonatal jaundice. Adv Pediatr 12: 121-187.
22. Maisels MJ (2006) What's in a name? Physiologic and pathologic jaundice: the conundrum of defining normal bilirubin levels in the newborn. Pediatrics 118: 805-807.
23. Maisels MJ, Bhutani VK, Bogen D, Newman TB, Stark AR, et al. (2009) Hyperbilirubinemia in the newborn infant > or =35 weeks' gestation: an update with clarifications. Pediatrics 124: 1193-1198.
24. Ronald W and Bhutani V (2016) Evaluation of Unconjugated Hyperbilirubinemia in Term and Late Preterm Infants. UpToDate..