



Hyperbilirubinemia in Neonates: Types, Causes, Clinical Examinations, Preventive Measures and Treatments: A Narrative Review Article

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Abstract

Background: Hyperbilirubinemia, or jaundice, is a life threatening disorder in newborns. It is a multifactorial disorder with many symptoms. Generally, the physiological jaundice is the most prevalent type however in some regions pathological jaundice is also common. This review article focuses on a brief introduction to jaundice, its types and causes, measuring the bilirubin level, clinical approaches towards hyperbilirubinemia, different precautionary measures for the parents of babies suffering from hyperbilirubinemia and different remedial therapeutic measures for its treatment.

Methods: The main databases including Scopus, Pubmed, MEDLINE, Google scholar and Science Direct were researched to obtain the original papers related to the newborns' hyperbilirubinemia. The main terms used to literature search were "newborns' hyperbilirubinemia", "newborns' jaundice", "Physiological Jaundice" and "Pathological Jaundice". The timeframe included the obtained articles was from 1952 to 2015.

Results: Neonatal jaundice due to breast milk feeding is also sometimes observed. Hemolytic jaundice occurs because of the incompatibility of blood groups with ABO and Rh factors, when the fetus and mother blood groups are not compatible and the fetus blood crosses the barrier of the umbilical cord before birth causing fetus blood hemolysis owing to severe immune response.

Conclusion: Jaundice is easily diagnosable however require quick and on the spot treatment. If not treated properly, it leads to many complications. Currently the treatment options for jaundice include photo therapy, chemotherapy, and vaccinations.

Keywords: Hyperbilirubinemia, Immunoglobulin, Bilirubinometer, Exchange transfusion

Introduction

One of the most prevalent clinical conditions in is hyperbilirubinemia (1). Neonatal hyperbilirubinemia is a common clinical problem encountered during the neonatal period, especially in the first week of life (2, 3). Nearly 8% to 11% of neonates develop hyperbilirubinemia. When the total serum bilirubin (TSB) rises above the 95th percentile for age (high-risk zone) during the first week of life, it will be considered as hyperbilirubinemia (4, 5).

Between 60%-80% of healthy infants are expected to present with idiopathic neonatal jaundice (6). Neonatal jaundice is the discoloration of skin and sclera color to yellowish in a newborn by bilirubin (7). Therefore it can create concern in the physician and anxiety in the parents. According to National Neonatal-Perinatal Database (NNPD) the incidence of neonatal hyperbilirubinemia in in-house live-births is 3.3%, while in extramural admissions morbidity due to hyper-

bilirubinemia accounted for 22.1% (8). In neonates, the dermal icterus is first noted in the face and when the bilirubin level rises, it proceeds to the body and then to the extremities. This condition is common in 50%-60% of newborns in the first week of life (8).

Bilirubin is not merely a nuisance molecule that has dire consequences, but bilirubin such as uric acid is an important antioxidant circulating in biologic system of neonate (9-11). However, high bilirubin levels can be toxic for central nervous system development and may cause behavioral and neurological impairment (Neurotoxicity or Kernicterus) even in term newborns (12-14). Five to ten percent of newborns developed jaundice required the management of hyperbilirubinemia (15). Neonatal jaundice may be on account of different parameters such as birth weight, gestational age, premature rupture of membranes, maternal infectious diseases or other illness during pregnancy, having different sources of origin, hence having different types (16).

The main causes of increased bilirubin mostly are: race, genetic polymorphisms; inherited and acquired defects e.g. spherocytosis, Gilbert's syndrome, Najjar 1 and 2 Molecular genetics studies have shown the correlations between neonates hyperbilirubinemia and different genetic variations which can change in enzyme activity. For example variations in the uridine 5'-diphosphate glucuronosyltransferase 1A1 (UGT1A1) gene may cause decreased enzyme activity in neonates and adults which leads to the unconjugated bilirubin accumulation. Also the variation in the organic anion transporter 2 (OATP2) gene may result in severe hyperbilirubinemia in neonates (17, 18). Variations of 388 G>A (Asp130Asn, rs2306283), 521 T>C (Val174Ala, rs4149056), 463 C>A (Pro155Thr, rs11045819) of the solute carrier organic anion transporter family member 1B1 (SLCO1B1) gene which encodes the hepatic solute carrier organic anion transporter 1B1, a putative bilirubin transporter, may dispose subjects to newborns hyperbilirubinemia by the limitation of hepatic bilirubin uptake (19-21). Furthermore, in a genome wide association study, two polymorphisms of SLCO1B3 gene

(rs17680137 C>G and rs2117032 C>T) were observed to have a strong association with serum bilirubin levels and to contribute to idiopathic mild unconjugated hyperbilirubinemia in healthy adults (22, 23).

Search Method

The following databases were searched in this study: Scopus, Pubmed, MEDLINE, Google scholar and Science Direct. The main terms used to literature search were "newborns' hyperbilirubinemia", "newborns' jaundice", "Physiological Jaundice" and "Pathological Jaundice". The timeframe included the obtained articles was from 1952 to 2015.

Types of Hyperbilirubinemia

Several types of Bilirubinemia have been reported in neonates including physiological jaundice, pathological jaundice, jaundice due to breastfeeding or breast milk and hemolytic jaundice including three subtypes due to Rh factor incompatibility, ABO blood group incompatibility and Jaundice associated with Glucose-6-phosphate dehydrogenase (G6PD) deficiency (24).

Physiological Jaundice

It is the most abundant type of newborn hyperbilirubinemia, having no serious consequences (25). Neurodevelopmental abnormalities including as athetosis, loss of hearing, and in rare cases intellectual deficits, may be related to high toxic level of bilirubin (26). Jaundice attributable to physiological immaturity which usually appears between 24-72 h of age and between 4th and -5th days can be considered as its peak in term neonates and in preterm at 7th day, it disappears by 10-14 days of life (27). Unconjugated bilirubin is the predominant form and usually its serum level is less than 15 mg/dl (28). Based on the recent recommendations of the AAP, bilirubin levels up to 17-18 mg/dl may be accepted as normal in term of healthy newborns (15).

Pathological Jaundice

Bilirubin levels with a deviation from the normal range and requiring intervention would be described as pathological jaundice (25). Appearance of jaundice within 24 h due to increase in serum bilirubin beyond 5 mg/dl/day, peak levels higher than the expected normal range, presence of clinical jaundice more than 2 weeks and conjugated bilirubin (dark urine staining the clothes) would be categorized under this type of jaundice.

Breast Feeding and Breast Milk Jaundice

Exclusively infants with breastfeeding have a different physiological pattern for jaundice compared with artificially feed babies (24). Jaundice in breast fed babies usually appears between 24-72 h of age, peaks by 5-15 days of life and disappears by the third week of life. Higher bilirubin levels have been reported in these infants (29). In case of breastfed newborns, mild jaundice may take 10-14 days after birth or may reoccur during the breast feeding period (30). Very large amounts of bilirubin rarely accumulate in the blood and cause cerebral lesions, a situation known as nuclear jaundice (31). These cuts may be followed by hearing loss, mental retardation, and behavioral disorders. A mild clinical jaundice has been observed in one third of all breastfed babies in the third week of life, which may persist for 2 to 3 months after birth in a few babies (32). Decreased frequency of breastfeeding is associated with exaggeration of physiological jaundice. One of the significant procedures to manage the jaundice in a term healthy baby is the mothers' encouragement to breastfeed their babies at least 10-12 times per day (33).

Hyperbilirubinemia is also associated with breast milk of mother in neonates (34). About 2%-4% of exclusively breastfed babies have jaundice in excess of 10 mg/dl in the third week of life. These babies in the third week of life with bilirubin serum levels higher than 10mg/dl should be considered for prolonged jaundice (35). A diagnosis of breast milk jaundice should be investigated if the serum bilirubin is predominantly unconjugated, other causes of prolonged jaundice have been eliminated and the infant is in good

health, vigorous and feeding well and gaining weight adequately (36). Mothers should be advised to continue breastfeeding at more frequent intervals and bilirubin levels usually diminish gradually. Discontinuity of breastfeeding is not recommended unless levels exceed 20 mg/dl (37).

Hemolytic Jaundice

The most common causes of hemolytic jaundice include (a) Rh hemolytic disease, (b) ABO incompatibility and (c) Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and minor blood group incompatibility.

(A) Rh Factor Hemolytic Disease

Rhesus hemolytic disease of the newborns (RHDN) results from maternal red-cell alloimmunization (38). Maternal antibodies are produced against the fetal red blood cells, when fetal red blood cells are positive for a certain antigen, usually at what time a baby having Rh positive born to an Rh-negative mother (21) (and Rh-positive father), then maternal immunoglobulin (IgG) antibodies might cross the placenta into the fetal circulation and cause a wide variety of symptoms in the fetus, ranging from mild to severe hemolytic anaemia and fetal hydrops (39, 40). To facilitate early treatment in neonates who are dubitable to have Rh factor, a blood group and Rh typing, DCT, PCV (packed cell volume) and serum bilirubin on cord blood should be performed. A reticulocyte count should be sent before the first exchange transfusion (ET). Vigorous phototherapy is required immediately after the birth and it should be continued until a level, which is 5 mg/dl less than the level estimated for exchange blood transfusion (41). In preterm babies, lower values of intervention for treatment of Rh hemolytic disease have been demonstrated. Phototherapy and exchange blood transfusion are recommended when a level is greater than 0.5% and 1% birth weight (kg) respectively (29). Eight intravenous immunoglobulin (IVIG) can be used in a dose of 500 mg/kg 12 hourly x 2 doses after the first ET. After the first ET starting of Pheno-barbitone 5 mg/kg/day x 5 may be recommended (24).

(b) ABO Incompatibility

The incidence of the incompatibility of the ABO blood groups of the mother and fetus, when the mother has the blood group O and the newborn has the A or B blood group, is 15-20% of all pregnancies (42). Babies with O-blood group mothers should be closely checked for and discharged after 72 h. Routine cord blood screening is not recommended for newborns with O-group mothers (43). Jaundice owing to ABO incompatibility usually appears 24 h after the birth. In the presence of significant jaundice or jaundice appearing within 24 h, the work up for pathological jaundice should be done (44). Intensive phototherapy is advised at SB 12-17 mg/dl depending upon postnatal age of the baby. Exchange blood transfusion is indicated at TSB. The weight at birth as a criterion for phototherapy and ET may be used for preterm newborns (45).

(c) Jaundice Associated With G6PD Deficiency

Deficiency, hereditary spherocytosis, and minor group incompatibilities should be managed similar to ABO incompatibility. G6PD, most common enzymopathy, is the deficiency of an enzyme in RBCs (46). It is the most vital disease of the pathway of hexose monophosphate (47). Investigations for G6PD deficiency should be considered in infants with severe jaundice in a family with a history of significant jaundice or in a geographic origin associated with G-6-PD deficiency (48, 49). Decreased bilirubin conjugation resulted from variation in the UGT1A1 and OATP2 genes play an important role in the progression of hyperbilirubinemia in G6PD deficient newborns (17).

Clinical Examination of Jaundice

Originally described by Kramer (33), dermal staining of bilirubin may be used as a clinical guide to the level of jaundice. Dermal staining in newborns progresses in a cephalo-caudal direction (50). The newborn should be examined in good daylight. The physician should pale the skin by digital pressure and the underlying color of skin and subcutaneous tissue should be noted.

Newborns who are detected the yellow skin beyond the thighs should have an urgent laboratory confirmation for bilirubin levels. Clinical assessment is unreliable if a newborn has been receiving phototherapy and has dark skin (51).

Measurement of Bilirubin Levels

Bilirubin level can be checked through biochemical method, Bilimeter or transcutaneous bilirubinometer (52-56).

Biochemical

The gold standard method for bilirubin estimation is the total and conjugated bilirubin assessment based on the van den Bergh reaction (57, 58).

Bilimeter

Spectrophotometry is the base of Bilimeter and it assesses total bilirubin in the serum. Because of the predominant unconjugated form of bilirubin, this method has been found a useful method in neonates.

Transcutaneous Bilirubinometer

This method is noninvasive and is based on the principle of multi wavelength spectral reflectance from the bilirubin staining in the skin (59). The accuracy of the instrument may be affected by variation of skin pigmentation and its thickness (60).

Clinical Approach to Jaundice

The initial step in evaluation of any newborn for jaundice is to differentiate between physiological and pathological jaundice. A helpful algorithm as adapted by AAP (2004b) (61) is as follows.

Dependency on Newborn Period or Preterm

Preterm intervention values are different and depend on the degree of prematurity and birth weight (62-64).

Evidence of Hemolysis

Onset of jaundice within 24 h, presence of pallor and hydrops, presence of hepatosplenomegaly, presence of hemolysis on the smear of peripheral blood, increased count of reticulocyte (>8%),

rapid rise of bilirubin (>5 mg/dl in 24 h or >0.5 mg/dl/hr) or a family history of considerable jaundice should create a suspicion of hemolytic jaundice (65).

Instructions and Precautionary Measure for Parents during Physiological Jaundice

The benign nature of jaundice should be explained and demonstrated to the parents. The mother should be encouraged to breast-feed her baby frequently and exclusively, at least eight to twelve times per day for initial several days, with no top feeds or glucose water whatsoever (66-68). Mother should be told to bring the baby to the hospital if the color on the legs looks as yellow as the face.

Any newborn discharged before 48 h of life should be evaluated again in the next 48 h for breastfeeding sufficiency and development of jaundice (3).

Management of pathological Jaundice

Confirmatory serum bilirubin level assessment is recommended for infants when they are noted to have yellow skin color outside of the thighs. The American Academy of Pediatrics (AAP) has laid down criteria for managing babies with bilirubin in the pathological range. Jaundice appearing within 24 h should be managed as hemolytic jaundice. The following investigations for all infants with bilirubin levels in the range of phototherapy including: baby's blood group, Rh typing and DCT (if Rh factor is absent in mother or mother has O blood group); packed cell volume (PCV); peripheral blood smear (PBS) for checking hemolysis and morphology of red blood cell; reticulocyte count and G6PD estimation (if indicated) (61). Any hemolytic cause of jaundice is done by these assessments. An inability to see a decrease in bilirubin level to 1-2 mg/dL after 4-6 h and/ or to keep the bilirubin below the exchange transfusion level has been defined as failure of phototherapy. However, irrespective of the bilirubin level, an exchange transfusion (ET) may be performed at the smallest doubt about bilirubin encephalopathy (69).

Treatment Options for Jaundice

The treatment options for jaundice include phototherapy further subdivided to conventional, intensive and exchange transfusion, and pharmacological treatment subdivided to phenobarbitone, intravenous immunoglobulins (IVIG), met-alloporphyrins and follow up remedies (70).

Phototherapy

Hyperbilirubinemia can be treated easily without or with a minimal adverse effect with phototherapy (71, 72). The efficacy of phototherapy depends on surface area exposed to phototherapy: Double surface phototherapy may be more effective than single surface phototherapy (73). Spectrum of light source: Special blue tubes with the mark F20T12/BB should be used rather than F20T12/B lights and Irradiance or energy output may be increased in a phototherapy unit by lowering the distance of the neonate to within 15-20 cm (74, 75). Continuous phototherapy is better than intermittent phototherapy. Phototherapy should not be interrupted except during breastfeeding or nappy change (40, 76-80).

(a) Conventional Phototherapy

One can use conventional or fiber-optic phototherapy units provided jaundice is non-hemolytic or its progression is slow.

(b) Intensive Phototherapy

In the circumstances including hemolytic jaundice, rapidly increasing bilirubin, or ineffectiveness of a conventional unit, using of intensive phototherapy is warranted. Placing the baby on the bili-blanket and using additional overhead phototherapy units contain blue lights and then lowering the phototherapy units to within a distance of 15-20 cm are two significant remedies (81).

(c) Exchange Transfusion

Through exchange transfusion bilirubin and hemolytic antibodies are removed (82).

(a) ***Rh Isoimmunization***: Always, Blood using for exchange transfusion should be negative Rh isoimmunization, negative for Rh factor. O (Rh)

negative packed cells suspended in AB plasma will be the best choice. O (Rh) negative whole blood or cross-matched baby's blood group (Rh negative) may also be used in an emergency (83, 84).

(b) **ABO Incompatibility:** Only O-blood group should be used for exchange transfusion in newborns with ABO incompatibility. The best choice would be O group (Rh compatible) packed cells which are suspended in O group/AB plasma whole blood (Rh compatible with baby).

(c) **Other situations:** In case of the Cross-matched with baby's blood group blood volume used or double volume exchange should be kept in mind.

(i) **Blood Volume Used:** Partial exchange is done at birth in Rh hemolytic disease: 50-ml/ kg of packed cells.

(ii) **Double Volume Exchange:** $2 \times (80-100 \text{ ml/kg}) \times \text{birth weight (kg)}$

Pharmacological Treatment

Pharmacological treatment of neonatal jaundice can further be categorized into different subheadings such as phenobarbitone, Intravenous immunoglobulins and Metalloporphyrins etc. (35, 85-87).

(a) Phenobarbitone

Bilirubin processing including hepatic uptake, conjugation and its excretion are ameliorated by this agent thus helps in decreasing level of bilirubin. However the effect of phenobarbitone is not rapid and takes time to show. When used for 3-5 days in a dose of 5 mg/kg after birth prophylactically, it has shown to be effective in babies with hemolytic disease, extravasated blood and in pre-term without any significant side effects. There is a huge literature documenting efficacy and mechanism of action and complications of treatment for Phenobarbital (88-94).

(b) Intravenous Immunoglobulin (IVIG)

High dose IVIG (0.5-1 gr/kg) has shown to be effective in decreasing the needs of exchange transfusion and phototherapy in babies with Rh hemolytic disease (95-102).

(c) Metalloporphyrins

These compounds are still experimental but showing promising results in various hemolytic

and non-hemolytic settings without significant side effects (88, 103-107).

(d) Follow-up

Babies having roughly 20 mg/dl serum bilirubin and that requiring exchange transfusion should be kept under follow-up in the high risk clinic for neurodevelopmental outcome (61, 108). Hearing assessment (Brainstem Evoked Response Audiometry (BAER)) should be done at 3 months of corrected age (109).

Recent Advances

Hour-specific bilirubin nomograms have been constructed based on routine pre-discharge bilirubin assessment (81, 110, 111). These charts are useful in predicting hyperbilirubinemia based on a bilirubin level done after 24 h of age. However the mentioned charts are prepared based on infants born in the West and probable need to be assessed and validated on Asian infants or on regional basis before they can be used for routine newborn care.

Conclusion

Hyperbilirubinemia is more severe in newborns. Therefore precautionary measure should be adopted by both parents, and clinicians to diagnose and treat the disease properly. Government and public health organizations should arrange seminars, workshops and trainings for mothers regarding neonatal jaundice. Medical scientists should search for new treatments and preventive measures having no side effects and capable of recovering babies more speedily. Partners should screen their ABO blood groups as well as Rh factor before marriage. Consanguineous marriages should be avoided.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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References

1. Olusanya BO, Osibanjo FB, Slusher TM (2015). Risk factors for severe neonatal hyperbilirubinemia in low and middle-income countries: a systematic review and meta-analysis. *PLoS One*, 10(2): e0117229.
2. Bhutani VK, Zipursky A, Blencowe H, Khanna R, Sgro M, Ebbesen F (2013). Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels. *Pediatr Res*, 1:86-100.
3. American Academy of Pediatrics Practice Parameter (1994). Management of hyperbilirubinemia in the healthy term newborn. *Pediatrics*, 94: 558-65.
4. Burke BL, Robbins JM, Bird TM, Hobbs CA, Nesmith C, Tilford JM (2009). Trends in hospitalizations for neonatal jaundice and kernicterus in the United States, 1988–2005. *Pediatrics*, 123: 524–32.
5. Young Infants Clinical Signs Study Group (2008). Clinical signs that predict severe illness in children under age 2 months: a multicentre study. *Lancet*, 371(9607): 135-42.
6. Chou RH, Palmer RH, Ezhuthachan S, et al. (2003). Management of hyperbilirubinemia in newborns: measuring performance by using a benchmarking model. *Pediatrics*, 112:1264–73.
7. Ogunfowora OB, Daniel OJ (2006). Neonatal jaundice and its management: Knowledge, attitude and practice of community health workers in Nigeria. *BMC Public Health*, 6:19.
8. Schneider AP (1986). Breast milk jaundice in the newborn: A real entity. *JAMA*, 255(23): 3270-74.
9. Nag N, Halder S, Chaudhuri R, Adhikary S, Mazumder S (2009). Role of bilirubin as antioxidant in neonatal jaundice and effect of ethanolic extract of sweet lime peel on experimentally induced jaundice in rat. *IJBB*, 46:73–78.
10. Yousefi M, Rahimi H, Barikbin B, Toossi P, Lotfi S, Hedayati M, et al (2011). Uric acid: a new antioxidant in patients with pemphigus vulgaris. *IJD*, 56(3): 278–281.
11. Barikbin B, Yousefi M, Rahimi H, Hedayati M, Razavi SM, Lotfi S (2011). Antioxidant status in patients with lichen planus. *CED*, 36(8): 851–54.
12. Paludetto R, Mansi G, Raimondi F, Romano A, Crivaro V, Bussi M, D'Ambrosio G (2002). Moderate hyperbilirubinemia induces a transient alteration of neonatal behavior. *Pediatrics*, 110: e50.
13. Boo NY, Ishak S (2007). Prediction of severe hyperbilirubinaemia using the Bilicheck transcutaneous bilirubinometer. *JPOCH*, 43: 297-302.
14. Nass RD, Frank Y (2010). *Cognitive and Behavioral Abnormalities of Pediatric Diseases*. 1st ed. Oxford University Press.
15. Gartner LM, Lee KS (1999). Jaundice in the breast-fed infant. *Clin Perinatol*, 26:431–45.
16. Mesic I, Milas V, Medimurec M, Rimar Z (2014). Unconjugated pathological jaundice in newborns. *Coll Anthropol*, 38(1): 173-8.
17. D'Silva S, Colah RB, Ghosh K, Mukherjee MB (2014). Combined effects of the UGT1A1 and OATP2 gene polymorphisms as major risk factor for unconjugated hyperbilirubinemia in Indian neonates. *Gene*, 547(1):18-22.
18. Huang MJ, Kua KE, Teng HC, Tang KS, Weng HW, Huang CS (2004). Risk factors for severe hyperbilirubinemia in neonates. *Pediatr Res*, 56(5):682-9.
19. Watchko JF, Lin Z (2010). Exploring the genetic architecture of neonatal hyperbilirubinemia. *Semin Fetal Neonatal Med*, 15:169–175.
20. Xu LY, He YJ, Zhang W, Deng S, Li Q, Zhang WX, et al. (2007). Organic anion transporting polypeptide-1B1 haplotypes in Chinese patients. *Acta Pharmacol Sin*, 28:1693–97.
21. Tirona RG, Leake BF, Merino G, and Kim RB (2001). Polymorphisms in OATP-C: identification of multiple allelic variants associated with altered transport activity among European- and African-Americans. *J Biol Chem*, 276:35669–35675.

22. Sanna S, Busonero F, Maschio A, McArdle PF, Usala G, Dei M, et al (2009). Common variants in the SLCO1B3 locus are associated with bilirubin levels and unconjugated hyperbilirubinemia. *Hum Mol Genet*, 18:2711–8.
23. Alencastro de Azevedo L, Reverbel da Silveira T, Carvalho CG, Martins de Castro S, Giugliani R, Matte U (2012). UGT1A1, SLCO1B1, and SLCO1B3 polymorphisms vs. neonatal hyperbilirubinemia: is there an association? *Pediatr Res*, 72(2):169-73.
24. Mishra S, Agarwal R, Deorari AK, Paul VK (2008). Jaundice in the newborns. *Indian J Pediatr*, 75(2): 157-163.
25. Boyd S (2004). Treatment of physiological and pathological neonatal jaundice. *Nursing Times*, 100(13): 40-43.
26. Clarkson JE, Cowan JO, Herbison GP (1984). Jaundice in full term healthy neonates: A population study. *Aust Paediatr J*, 20:303-8.
27. Dennerly PA, Seidman DS, Stevenson DK (2001). Neonatal hyperbilirubinemia. *NEJM*, 344(8): 581-290.
28. Maisels MJ, Gifford K (1983). Neonatal jaundice in full-term infants. Role of breastfeeding and other causes. *AJDC*, 137:561–2.
29. Alcock GS, Liley H (2002). Immunoglobulin infusion for isoimmune haemolytic jaundice in neonates. *CDSR*, 3: CD003313.
30. Atkinson LR, Escobar GJ, Takyama, JI, Newman TB (2003). Phototherapy use in jaundiced newborns in a large managed care organization: do clinicians adhere to the guideline? *Pediatrics*, 111: e 555.
31. Hansen TW (2003). Recent advances in the pharmacotherapy for hyperbilirubinemia in the neonate. *Exp Opin Pharmacother*, 4(11): 1939-1948.
32. Winfield CR, MacFaul R (1978). Clinical study of prolonged jaundice in breast and bottle fed babies. *Arch Dis Child*, 53: 506-7.
33. Kramer LI (1969). Advancement of dermal icterus in jaundiced newborn. *AJDC*, 118: 454-8.
34. Shapiro-Mendoza C (2006). Risk factors for neonatal morbidity and mortality among “healthy” late preterm newborns. *Semin Perinatol*, 30: 54-60.
35. Dennerly PA (2002). Pharmacological interventions for the treatment of neonatal jaundice. *Semin Neonatology*, 7: 111-119.
36. Maruo Y, Nishizawa K, Sato H, Sawa H, Shimada M (2000). Prolonged unconjugated hyperbilirubinemia associated with breast milk and mutations of the bilirubin uridine diphosphate- glucuronosyltransferase gene. *Pediatrics*, 106(5): 1-4.
37. Maisels MJ (1998). Jaundice. In: Taeguh, H.W., Ballard, R.A. and Avery, M.E. (eds). Schaffers and Avery’s Diseases of Newborn (7th ed.). Philadelphia: WB Saunders Company. pp. 603-708.
38. Al-Swaf FB, Jumaa RS, Saeed IS (2009). Hemolytic disease of newborn due to ABO incompatibility. *Tikrit Medical Journal*, 15(2): 70-78.
39. Stockman, JA (2001). Overview of the state of the art of Rh disease: history, current clinical management, and recent progress. *J Pediatr Hematol Oncol*, 23(8):554-62.
40. Bowman J (2003). Thirty-five years of Rh prophylaxis. *Transfusion*, 43:1661-6.
41. Van Kamp IL, Klumper FJ, Oepkes D, Meerman RH, Scherjon SA, Vandenbussche FP, et al (2005). Complications of intrauterine intravascular transfusion for fetal anemia due to maternal red-cell alloimmunization. *Am J Obstet Gynecol*, 192(1): 171-7.
42. Murray NA, Roberts IA (2007). Haemolytic disease of the newborn. *ADC Fetal Neonatal Ed*, 92: 83-8.
43. Yigit S, Gursay T, Kanra T, et al (2005). Whole blood versus red cells and plasma for exchange transfusion in ABO haemolytic disease. *Trans Med*, 15: 313-8.
44. Yaseen H, Khalaf M, Rashid N, Darwich M (2005). Does prophylactic phototherapy prevent hyperbilirubinemia in neonates with ABO incompatibility and positive Coombs' test? *J Perinatol*, 25: 590-4.
45. Kaplan M, Na'amad M, Kenan A, Rudensky B, Hammerman C, Vreman HJ, Wong RJ, Stevenson DK (2009). Failure to predict hemolysis and hyperbilirubinemia by IgG subclass in blood group A or B infants born to group O mothers. *Pediatrics*, 123(1): 132-7.
46. Moiz B, Nasir A, Khan SA, Kherani SA, Qadir M (2012). Neonatal hyperbilirubinemia in infants with G6PD c.563C > T variant. *BMC Pediatrics*, 12: 126-133.
47. Marzban A, Mosavinasab N (2008). Correlation between hemolysis and jaundice in Glucose 6-

- Phosphate Dehydrogenase deficient neonates. *Acta Medica Iranica*, 47(5): 379-83.
48. Kaplan M, Hammerman C (1998). Severe neonatal hyperbilirubinemia. A potential complication of glucose-6-phosphate dehydrogenase deficiency. *Clin Perinatol*, 25(3): 575-90.
49. Bhutani VK, Johnson L, Sivieri ME (1999). Predictive ability of a predischARGE hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*, 103(1): 6-16.
50. Cashore WJ (2000). Bilirubin and jaundice in the micropremie. *Clin Perinatol*, 27: 171-9.
51. Johnson L, Bhutani VK (1998). Guidelines for management of the jaundiced term and near term infant. *Clin Perinatol*, 25: 555-574.
52. Watson D, Rogers JA (1961). A study of six representative methods of plasma bilirubin analysis. *J Clin Pathol*, 14: 271-8.
53. Yamanouchi I, Yamauchi Y, Igarashi I (1980). Transcutaneous bilirubinometry: preliminary studies of noninvasive transcutaneous bilirubin meter in the Okayama National Hospital. *Pediatrics*, 65:195-202.
54. Maisels MJ, Ostrea EM, Touch S, Clune SE, Cepeda E, Kring E, et al (2004). Evaluation of a new transcutaneous bilirubinometer. *Pediatrics*, 113: 1628-35.
55. Gohmann K, Roser M, Rolinski B, Kadow I, Muller C, Goerlach-Graw A, et al (2005). Bilirubin measurement for neonates: Comparison of 9 frequently used methods. *Pediatrics*, 117(4): 1174-85.
56. Puppulwar PV, Goswami K, Dhok A (2012). Review on "Evolution of Methods of Bilirubin Estimation". *IOSR-JDMS*, 1(3): 17-18.
57. Royal Prince Alfred Hospital (2003). Haemolytic jaundice, Rhesus isoimmunization. RPA Newborn care guidelines: Royal Prince Alfred Hospital, Sydney Australia.
58. Bosschaart N, Kok JH, Newsum AM, Ouwenne DM, Mentink R, van Leeuwen TG, et al (2012). Limitations and opportunities of transcutaneous bilirubin measurement. *Pediatrics*, 129: 689-97.
59. Krishnasamy M, Bakri DR (2009). Non-invasive, hand held transcutaneous bilirubinometer. Medical Development Division, Ministry of Health, Malaysia.
60. Robertson A, Kazmierczak S, Vos P (2002). Improved transcutaneous bilirubinometry: comparison of SpectRx Bilicheck and Minolta jaundice meter JM-102 for estimating total serum in a normal newborn population. *J Perinatol*, 22(1):12-14.
61. American Academy of Pediatrics (2004b). Clinical Practice Guideline: Subcommittee on Hyperbilirubinemia, Management of Hyperbilirubinemia in the newborn infant 35 or more week of gestation. *Pediatrics*, 114(1): 297-316.
62. Watchko JF, Maisels MJ (2003). Jaundice in low birth weight infants: pathobiology and outcome. *ADC Fetal Neonatal Ed*, 88: F455-8.
63. Okwundu CI, Okoromah CAH, Shah PS (2012). Prophylactic phototherapy for preventing jaundice in preterm or low birth weight infants. *Cochrane Database Syst Rev*, 2012(1): CD007966.
64. Maisels MJ, Watchko JF, Bhutani VK, Stevenson DK (2012). An approach to the management of hyperbilirubinemia in the preterm infant less than 35 week of gestation. *J Perinatol*, 32: 660-4.
65. Frank JE (2005). Diagnosis and management of G6PD deficiency. *Am Fam Phys*, 72(7): 1277-1282.
66. Engle WD, Jackson GL, Sendelbach D, Manning D, Frawley W (2002). Assessment of a transcutaneous device in the evaluation of neonatal hyperbilirubinemia in a primarily Hispanic population. *Pediatrics*, 110: 61-67.
67. Schumacher R (2002). Transcutaneous bilirubinometry and diagnostic tests: "the right job for the tool." *Pediatrics*, 110: 407-408.
68. Ip S, Glick S, Kulig J, Obrien R, Sege R, Lau J (2003). *Management of Neonatal Hyperbilirubinemia*. Rockville, MD: US Department of Health and Human Services, Agency for Healthcare Research and Quality. AHRQ Publication 03-E011.
69. Kappas A, Drummond GS, Munson DP, Marshall JR (2001). Sn-mesoporphyrin interdiction of severe hyperbilirubinemia in Jehovah's Witness newborns as an alternative to exchange transfusion. *Pediatrics*, 108: 1374-7.
70. Ennever JF (1990). Blue light, green light, white light, more light: treatment of neonatal jaundice. *Clin Perinatol*, 17:467-81.
71. Cremer RJ, Perryman RW, Richards DH (1958). Influence of light on the hyperbilirubinaemia of infants. *Lancet*, 1:1094-7.

72. Brown AK, Kim MH, Wu PY, Bryla DA (1985). Efficacy of phototherapy in prevention and management of neonatal hyperbilirubinemia. *Pediatrics*, 75: 393–400.
73. Vecchi C, Donzelli GP, Migliorini MG, Sbrana G (1983). Green light in phototherapy. *Pediatr Res*, 17:461-3.
74. Tan KL (1989). Efficacy of fluorescent daylight, blue, and green lamps in the management of nonhemolytic hyperbilirubinemia. *J Pediatr*, 114:132-7.
75. Tan KL (1991). Phototherapy for neonatal jaundice. *Clin Perinatol*, 18: 423-39.
76. Amato M, Howald H, von Muralt G (1985). Interruption of breast-feeding versus phototherapy as treatment of hyperbilirubinemia in full-term infants. *Helvetica Paediatrica Acta*, 40:127–31.
77. Caldera R, Maynier M, Sender A, Brossard Y, Tortrat D, Galiay JC, Badoual J. (1993). The effect of human albumin in association with intensive phototherapy in the management of neonatal jaundice. *Arch Fre Pediatr*, 50: 399-402.
78. Maisels MJ (2001). Phototherapy—traditional and nontraditional. *J Perinatol*, 21(suppl 1): S93–7.
79. Seidman DS, Moise J, Ergaz Z, Laor A, Vreman HJ, Stevenson DK, Gale R (2000). A new blue light-emitting phototherapy device: A prospective randomized controlled study. *J Pediatr*, 136(6): 771-4.
80. Harris M, Bernbaum J, Polin J, Zimmerman R, Polin RA (2001). Developmental follow-up of breastfed term and near-term infants with marked hyperbilirubinemia. *Pediatrics*, 107: 1075–1080.
81. American Academy of Pediatrics (2004a). Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more week of gestation. *Pediatrics*, 114 (3): 297–316.
82. Royal Prince Alfred Hospital (2006). Transcutaneous bilirubinometers. RPA Newborn care guidelines, Royal Prince Alfred Hospital, Sydney Australia.
83. Hsia DYY, Allen FH, Gelliss SS, Drummond LK (1952). Erythroblastosis fetalis, VIII: studies of serum bilirubin in relation to kernicterus. *N Engl J Med*, 247:668-71.
84. Mollison PL, Cutbush M (1954). *Haemolytic disease of the newborn*. In: Gairdner D, ed. Recent Advances in Pediatrics. New York, NY: P Blakiston & Son, pp: 110.
85. Gabilan JC (1998). Pharmacologic treatment of neonatal jaundice. A new approach. *Archives de Pediatrie*, 5(11): 1274-8.
86. Cuperus FJ, Hafkamp AM, Hulzebos CV, Verkade HJ (2009). Pharmacological therapies for unconjugated hyperbilirubinemia. *Curr Pharm Des*, 15(25): 2927-38.
87. Kaseem LM, Abdelrahim MEA, Naguib HF (2013). Investigating the Efficacy and Safety of Silymarin in Management of Hyperbilirubinemia in Neonatal Jaundice. *Med Sci*, 2(2): 575-590.
88. Valaes T, Petmezaki S, Henschke C, Drummond GS, Kappas A (1994). Control of jaundice in preterm newborns by an inhibitor of bilirubin production: studies with tin-mesoporphyrin. *Pediatrics*, 93(1): 1–11.
89. Marie S, Cresteil T (1989). Phenobarbital-inducible gene expression in developing rat liver: relationship to hepatocyte function. *Biochimica et Biophysica Acta*, 1009(3): 221–8.
90. Shankaran S, Papile LA, Wright LL, Ehrenkranz RA, Mele L, Lemons JA, et al (1997). The effect of antenatal phenobarbital therapy on neonatal intracranial hemorrhage in preterm infants. *N Engl J Med*, 337(7): 466–471.
91. Shankaran S, Woldt E, Nelson J, Bedard M, Delaney-Black V (1996). Antenatal phenobarbital therapy and neonatal outcome. II: Neurodevelopmental outcome at 36 months. *Pediatrics*, 97(5): 649–52.
92. Hansen TW, Tommarello S (1998). Effect of phenobarbital on bilirubin metabolism in rat brain. *Biol Neonate*, 73(2): 106–11.
93. Crowther CA, Henderson-Smart DJ (2000). Phenobarbital prior to preterm birth for preventing neonatal periventricular haemorrhage. *Cochrane Database Syst Rev*, 2000; 2.
94. Whitelaw A (2001). Postnatal phenobarbitone for the prevention of intraventricular hemorrhage in preterm infants. *Cochrane Database Syst Rev*, 2001; 1. CD000164.
95. Sato K, Hara T, Kondo T, Iwao H, Honda S, Ueda K (1991). High-dose intravenous gammaglobulin therapy for neonatal immune haemolytic jaundice due to blood group incompatibility.

- patibility. *Acta Paediatrica Scandinavica*, 80: 163–6.
96. Rubo J, Albrecht K, Lasch P, Laufkotter E, Leitis J, Marsan D, et al (1992). High-dose intravenous immune globulin therapy for hyperbilirubinemia caused by Rh hemolytic disease. *J Pediatr*, 121: 93–7.
97. Ergaz Z, Arad I (1993). Intravenous immunoglobulin therapy in neonatal immune hemolytic jaundice. *J Perinat Med*, 21(3): 183–7.
98. Hammerman C, Kaplan M, Vreman HJ, Stevenson DK (1996). Intravenous immune globulin in neonatal ABO isoimmunization: factors associated with clinical efficacy. *Biol Neonate*, 70: 69–74.
99. Alpay F, Sarici SU, Okutan V, Erdem G, Ozcan O, Gokcay E (1999). High-dose intravenous immunoglobulin therapy in neonatal immune haemolytic jaundice. *Acta Paediatrica*, 88: 216–219.
100. Girish G, Chawla D, Agarwal R, Paul VK, Deorari AK (2008). Efficacy of two dose regimes of intravenous immunoglobulin in Rh hemolytic disease of newborn – a randomized controlled trial. *Indian Pediatrics*, 45: 653–9.
101. Smits-Wintjens VE, Walther FJ, Rath ME, Lindenburg IT, te Pas AB, Kramer CM, Oepkes D, Brand A, Lopriore E (2011). Intravenous immunoglobulin in neonates with rhesus hemolytic disease: a randomized controlled trial. *Pediatrics*, 127: 680–6.
102. Cortey A, Elzaabi M, Waegemans T, Roch B, Aujard Y (2014). Efficacy and safety of intravenous immunoglobulins in the management of neonatal hyperbilirubinemia due to ABO incompatibility: a meta-analysis. *Archives de Pédiatrie*, 21(9): 976–83.
103. Qato MK, Maines MD (1985). Prevention of neonatal hyperbilirubinaemia in non-human primates by Znprotoporphyrin. *Biochem J*, 226(1): 51–7.
104. Vreman HJ, Ekstrand BC, Stevenson DK (1993). Selection of metalloporphyrin heme oxygenase inhibitors based on potency and photoreactivity. *Pediatr Res*, 33(2): 195–200.
105. Kappas A, Drummond GS, Henschke C, Valaes T (1995). Direct comparison of Sn-mesoporphyrin, an inhibitor of bilirubin production, and phototherapy in controlling hyperbilirubinemia in term and near-term newborns. *Pediatrics*, 95(4): 468–74.
106. Valaes T, Drummond GS, Kappas A (1998). Control of hyperbilirubinemia in glucose-6-phosphate dehydrogenase-deficient newborns using an inhibitor of bilirubin production, Sn-mesoporphyrin. *Pediatrics*, 101(5): E1.
107. Martinez JC, Garcia HO, Otheguy LE, Drummond GS, Kappas A (1999). Control of severe hyperbilirubinemia in fullterm newborns with the inhibitor of bilirubin production Sn-mesoporphyrin. *Pediatrics*, 103(1): 1–5.
108. Facchini FP, Mezzacappa MA, Rosa IRM, Filho FM, Netto AA, Marba STM (2007). Follow-up of neonatal jaundice in term and late premature newborns. *Journal de Pédiatrie*, 83(4): 313–8.
109. Sharma P, Chhangani NP, Meena KR, Jora R, Sharma N, Gupta BD (2006). Brainstem Evoked Response Audiometry (BAER) in Neonates with Hyperbilirubinemia. *Indian J Pediatr*, 73 (5): 413–6.
110. Bhutani VK (2012). Jaundice Due to Glucose-6-Phosphate Dehydrogenase Deficiency. *Neo Rev*, 13(3): e166–79.
111. Kuboi T, Kusaka T, Kawada K, Koyano K, Nakamura S, Okubo K, et al (2013). Hour-specific nomogram for transcutaneous bilirubin in Japanese neonates. *Pediatr Int*, 55: 608–11.