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Case Report

Management of hyperbilirubinemia in near-term newborns according to American Academy of Pediatrics Guidelines: Report of three cases

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All neonates have a transient rise in bilirubin levels, and about 30-50% of infants become visibly jaundiced.[1,2] Most jaundice is benign; however, because of the potential brain toxicity of bilirubin, newborn infants must be monitored to identify those who might develop severe hyperbilirubinemia and, in rare cases, acute bilirubin encephalopathy or kernicterus. Ten percent of term infants and 25% of near-term infants have significant hyperbilirubinemia and require phototherapy.[3] The American Academy of Pediatrics (AAP) recommends procedures to reduce the incidence of severe hyperbilirubinemia and bilirubin encephalopathy, and to minimize the risks of unintended harm such as maternal anxiety, decreased breastfeeding, and unnecessary costs or treatment.[4]

The guidelines provide a framework for the prevention and management of hyperbilirubinemia in newborn infants of 35 weeks or more of gestational age(term and near-term newborns). This case report details the management of three newborns of 35 or more gestational age at the Siloam Lippo Cikarang Hospital, Tanggerang, West Java, Indonesia according to the AAP guidelines.

Case 1

A baby girl was born spontaneously to a 33-year-old mother at 40 week gestation with minor risk factors. The birth weight was 3350 g, birth length was 48 cm, and head circumference was 34 cm. The Apgar score was 9 at five minutes after birth and 10 at seven minutes. This was the mother's first pregnancy and both mother and baby had positive Rhesus blood group. The baby appeared to be jaundiced at 70 hours after birth with a total serum bilirubin (TBS) level of 12.9 mg/dl. She was breastfed exclusively and had no history of naftalene balls or drug exposure. At 120 hours after birth, the TSB level increased to 15.1 mg, but the baby was still active and had normal vital signs. By day 7, the TSB level had increased to 17.1 mg/dl (direct (D)/indirect (I) bilirubin = 0.1/17

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mg/dl), even though the G6PD level and OAE (Oto Acoustic Emission) were normal. According to the AAP guidelines, the TSB level was still below the critical level for phototherapy, so the baby was discharged without any specific treatment. The TSB level on the day after discharge was 16.6 mg/dl and the baby was clinically normal.

Case 2

A baby boy of 38-week-gestation was born by cesarean section due to a cephalopelvic disproportion. The baby's birth weight was 3220 g, the birth length was 48 cm, and the head circumference was 34 cm. The baby was classified as having minor risk factors with Apgar score of 8 at five minutes after birth, and 9 at seven minutes. The baby had the same blood type as the mother's, i.e., blood group O and Rhesus positive. It was the first pregnancy for the mother, 30 years old. The baby looked jaundiced at 70 hours old, but as the TSB level at 73 hours was 15.2 mg/dl (D/I = 0.1/15.1 mg/dl), he was discharged. The baby was breastfed and given hypoallergenic formula as needed. The baby returned for evaluation on day 7 and had a TSB level of 15.3 mg/dl (D/I = 0.1/15.2 mg/dl) with a normal G6PD level. Therefore, no intervention was needed and all that was required was assurance and education to the parents. On the next visit at nine days old, the TSB level was 12.9 mg/dl (D/I = 0.1/12.8 mg/dl) and an OAE examination revealed that this was within normal limits.

Case 3

A female newborn of 39 weeks gestation was born to a 32-year-old mother by vacuum extraction. The baby's birth weight was 3390 g, birth length 49 cm, and head circumference 34 cm. She had Apgar score of 8 at the first five minutes after birth and 9 at seven minutes. The baby had minor risk factors and was the third child of a mother without a history of miscarriage; she and the mother had the same blood type i.e. O an Rhesus positive. The TSB level measured at 43 hours after birth was 10.6 mg/dl (D/I = 0.1/10.5 mg/dl). The baby was sent home at two days old and was breastfed exclusively. Measurement of the TSB level at 91 hours gave a value of 17.1 mg/dl (D/I 0.1/17 mg/dl). The criterion for carrying out phototherapy at 91 hours after birth is a TSB level of $\geq$ 16.5 mg/dl. Since the baby was categorized as low risk (a healthy baby of >38 weeks gestation) with a TSB level above the critical level for intervention, the baby was treated with phototherapy. The baby's G6PD level was normal, Coomb's test was negative and the OAE examination was normal for both ears. The TSB level was measured again two days later and had decreased to 12.5 mg/dl (D/I = 0.1/12.5 mg/dl) and so the baby was discharged.

Discussion

Hyperbilirubinemia is defined as elevated bilirubin level (total serum bilirubin > 5 mg/dl) that can be identified as yellow color (jaundice) due to accumulation of bilirubin.[5] Bilirubin is the metabolism product of hemoglobin and other heme proteins. The initial breakdown product is unconjugated bilirubin (indirect bilirubin), which is found in the blood bound to albumin. When the albumin is saturated with bilirubin, excess unconjugated bilirubin can cross the blood-brain barrier as it is lipid soluble. Unconjugated bilirubin bound to albumin is conjugated in the liver (direct bilirubin) and is then excreted into the gut via the biliary tract. Some of this conjugated albumin-bound bilirubin is reabsorbed from the gut by enterohepatic circulation. Certain conditions can increase bilirubin production such as hemolytic disease, impaired liver uptake, bilirubin conjugation disturbance, and an increase in the enterohepatic cycle. These conditions maybe the cause of pathologic jaundice in newborns.[6]

In newborn infants, jaundice can be detected by blanching the skin with physical pressure, revealing the underlying color of the skin and subcutaneous tissue. The assessment of jaundice must be performed in a well-lighted room, preferably in daylight near a window. Jaundice is usually seen first in the face at a TSB level of > 4 mg/dl, and progresses caudally to the trunk and extremities. However, visual estimation of bilirubin levels from the degree of jaundice can lead to errors.[4] A transcutaneus bilirubin (TcB) or TSB measurement should be performed on every infant who is jaundiced during the first 24 hours after birth, or if the jaundice

appears excessive for the infant's age. Researchers have designed and evaluated several strategies for formally assessing the risk of severe neonatal hyperbilirubinemia and the AAP has recommended formal hyperbilirubinemia risk assessment for all newborns. Risk assessment strategies that provide an accurate estimation of risk can be used to target preventive care, such as further testing and closer follow-up for newborns at the greatest risk of developing severe neonatal hyperbilirubinemia and kernicterus. This strategy also avoids the cost and inconvenience of tests and follow-up for low-risk infants. Two strategies that have been investigated and recommended by the AAP include: 1) measuring bilirubin concentration and plotting the results on a normogram that displays bilirubin percentiles with respect to postnatal age in hours; and 2) systematically identifying clinical risk factors associated with severe hyperbilirubinemia (**Table 1**).[7] When either or both options are used, appropriate follow-up after discharge is essential.[4]

Table 1. Risk factors for development of severe hyperbilirubinemia in infants of 35 or more weeks gestation in approximate order of importance[4]

Major risk factors
- Predischarge TSB or TcB level in the high-risk zone
- Jaundice observed in the first 24 hours
- Blood group incompatibility with positive direct antiglobulin test;
- other known hemolytic disease
- Gestational age 35-36 weeks
- Previous sibling received phototherapy
- Cephalohematoma or significant bruising
- Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive.
- East Asian race.

Minor risk factors
- Predischarge TSB or TcB level is in the high intermediate-risk zone
- Gestational age 37-38 weeks
- Jaundice observed before discharge
- Previous sibling with jaundice
- Microsomic infant with diabetic mother
- Maternal age > 25 years old
- Male gender

Decreased risks (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance):
- TSB or TcB level is in the low-risk zone.
- Gestational age > 41 weeks.
- Exclusive breastfeeding
- Black race
- Discharged from hospital after 72 hours.

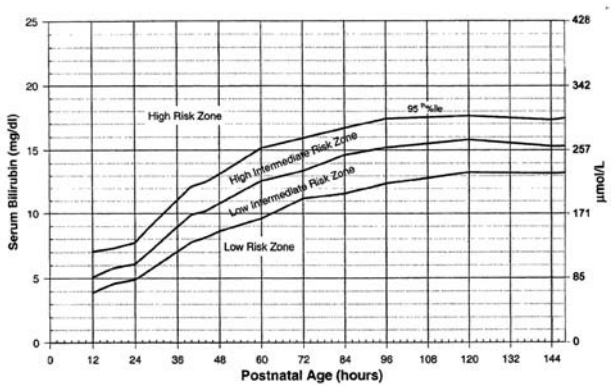

Figure 1. Hour-specific bilirubin nomogram. Predischarge bilirubin level, expressed as a risk zone on the nomogram, is used to predict the development of severe hyperbilirubinemia.[7]

In Case 1, the baby looked jaundiced from the feet to the chest area at 70 hours. The TSB level at that time was 12.9 mg/dl. According to the nomogram, the baby was in the low intermediate risk zone (**Figure 1**). No intervention was needed according to the guideline, hence the baby was discharged (**Figure 2**, we used the option of 3 mg/dl below those shown). The baby was in a lower risk group, she looked jaundiced at 70 hours and the TSB level cut off point was 14 mg/dl. According to the guideline, hospitalized infants of 35 or more weeks of gestation can be divided into three groups i.e. infants at lower risk ($\geq$ 38 weeks of gestation and well baby); infants at medium risk ($\geq$ 38 weeks of gestation + risk factors or 35-37 weeks of gestation, Apgar score 6/7, and well baby); infants at higher risk (35-37 weeks of gestation, Apgar score 6/7, + risk factors). These risk factors were isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or serum albumin level of < 3 g/dl (if measured).[4] An hour- specific bilirubin nomogram (**Figure 1**) that has been recommended as an approach for predicting neonatal hyperbilirubinemia was developed based on the hypothesis that early bilirubin values, expressed as a percentile with respectively to the infant's age in hours, are predictive of the infant's later bilirubin values, also expressed as a percentile with respectively to infant's age in hours (hereafter referred to as the hour-specific TSB).

Verger and colleagues[7] stated that if the biological factors that determine bilirubin production

and elimination when TSB levels peak 3-5 days after birth are also present in the first two days after birth, then the hour-specific TSB value measured prior to discharge are closely correlated with hour-specific value when at the peak TSB level. The concept was that this hour-specific bilirubin nomogram could be used like a pediatric growth chart, with the expectation that children starting out on a certain percentile track will stay on or near that percentile track as time passes.[7] If a baby stays in the high-risk zone (>P95), the possibility to stay in that zone is 39.5%. Moreover, if a baby is in the high-intermediate risk zone, there is the possibility that the TSB level will rise to more than P95 is 12.9%. If the baby is in the low to intermediate-risk zone (such as in Case 1), there is the possibility of TSB reaching more than P95 is 2.26%. [8]

In Case 2, the TSB level at 73 hours was 15 mg/dl (in the high intermediate-risk zone as shown in **Figure 1** but was still below the level where phototherapy is required (**Figure 2**). In Case 3, the TSB level at 43 hours was 10.6 mg/dl. According to the nomogram (**Figure 1**), these babies would stay in high intermediate-risk zone, and according to the phototherapy guideline (**Figure 2**), no intervention was needed. Although we used an option to do phototherapy of 3 mg/dl below the data shown (as stated in the guideline as an option), so the babies were discharged at that time.

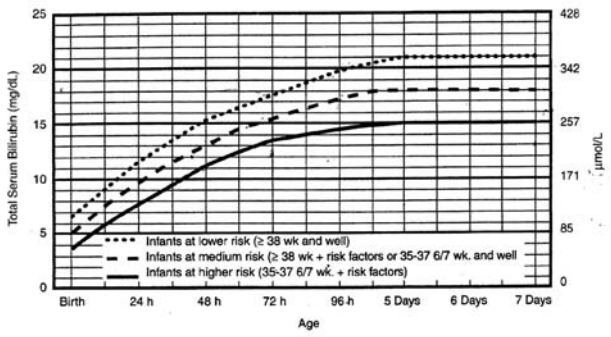

Figure 2. Guidelines for phototherapy in infants of 35 or more weeks gestation[4]

Table 2. Time of follow up examination for infants based on age at discharge[4]

Infant age at discharge	Time of follow up examination
Before 24 hours	72 hours
Between 24 and 48 hours	96 hours
Between 48 and 72 hours	120 hours

All infants should be examined by a qualified health care professional in the first few days after discharge to assess the condition of the infant; this examination should include noting the presence or absence of jaundice. The timing and location of this assessment depend on the length of stay in the nursery **(Table 2)**, and presence or absence of risk factors for hyperbilirubinemia.[4]

A report from Shaare Zadek Medical Center in Jerusalem, Israel, recommended that all babies should be seen within 2-4 days after being discharged from hospital? for the assessment of jaundice and the success of breastfeeding. In the case of males, less formal bilirubin evaluation occurs in the case of males during the home visit by the ritual circumciser (mohel). This visit is frequently a source of referral for hyperbilirubinemia because according to the Jewish ritual law, a baby should not be jaundiced at the time of ritual circumcision on the eighth day of life. This injunction extends to parents of baby girl as well. As a result, this population is aware of neonatal jaundice.[9]

In Case 3, the baby was sent home at 43 hour after birth and returned at 91 hours after birth. When the baby returned, he was hospitalized for phototherapy as determined by following the APP guidelines (**Figure 2;** healthy babys born at $\geq$ 38 weeks with a TSB level of $\geq$ 16.5 mg/dl at 91 hours after birth). In Cases 1 and 2, the TSB levels were still below the criteria level for phototherapy (we used an option to provide phototherapy at TSB level of 3 mg/dl below those shown). The hyperbilirubinemia readmission rate to the pediatric ward and NICU decreased by 38% in the first year after the Cedar-Sinai Medical Center, Los Angeles started using guidelines based on the AAP guidelines.[10]

In breastfed infants who require phototherapy, AAP recommends that breastfeeding should be continued if possible. It is also an option to temporarily interrupt breastfeeding and use formula instead. This can reduce bilirubin levels and/or enhance the efficacy of phototherapy. In breastfed infants who receive phototherapy, supplementation with expressed breast milk or formula is appropriate if the infant's intake seems inadequate, weight loss is excessive,

or the infant is dehydrated.[4] A paramount step in following these recommendations is to promote and support successful breastfeeding and explain clearly that jaundice associated with breastfeeding is caused by inadequate breastfeeding rather than assuming that jaundice is always associated with breastfeeding. When this information is used in explaining to a mother why her child is jaundiced, it certainly will reduce a mother's guilty feelings, support lactation, and prevent the vulnerable child syndrome in the future.[11] Our third case, who received phototherapy still continued to be breastfed and the mother also expressed breast milk at home.

Breast milk consumption is associated with neonatal hyperbilirubinemia. Intermediate hyperbilirubinemia (TSB 12 mg/dl) exists in 12.9% of exclusively breastfed infants and in 4% of infants who consume formula milk. Moreover, severe hyperbilirubinemia (TSB level 15 mg/dl) exists in 2% of breastfed infants and 0.3% of infants fed with formula milk. The cause of this condition is not well understood. There are some theories trying to explain the pathophysiology of this type of jaundice based on biochemistry. Breast milk contains 3 alpha, 20 beta-pregnandiol and has lipoprotein lipase activity which indicated by increased beta-glucuronidase. This 3-alpha, 20 beta-pregnandiol can prohibit bilirubin conjugation, while beta-glucuronidase can induce the readsorption of bilirubin from the gut. Furthermore, the increased fatty acid produced from triglyceride by lipase lipoprotein can disturb liver uptake and bilirubin conjugation. Hyperbilirubinemia asssociated with breast milk consumption can be divided into two types: early jaundice known as breastfeeding jaundice and late jaundice called breast milk jaundice. Breastfeeding hyperbilirubinemia is usually due to inadequate breastfeeding in the early postpartum period. Breast milk jaundice usually appears after one week in healthy and growing infants; 2-4% of these babies have a TSB level of >10 mg/dl at three weeks of age. It is not clear how these two types are correlated, but in babies with breast milk jaundice, there are two peaks in bilirubin level, one at day 4-5 and one at day 15-17. Fourteen percent of the siblings of these babies have also been reported to have prolonged indirect hyperbilirubinemia of unknown cause. Therefore, it seems likely that genetic and environment factors also play a role in this pathophysiology.[12-4]

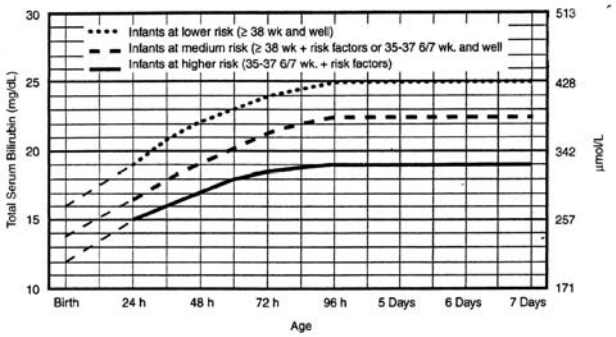

Figure 3. Guidelines for exchange transfusion in infants of 35 or more weeks gestation[4]

A TSB level that does not reduce or even increases after intensive phototherapy indicates the possibility of hemolytic disease. Exchange transfusion is recommended if the TSB level increases as shown in **Figure 3**.

For readmitted infants with a TSB level above the exchange level, it is recommended to repeat the TSB measurement every 2-3 hours and consider performing an exchange transfusion? if the TSB level remains above the critical level after intensive phototherapy for six hours. Immediate exchange transfusion is recommended if there are signs of acute bilirubin enchephalopahty (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if the TSB level is $\geq$ 5mg/dl above this line.

Kernicterus, although infrequent, has significant mortality of at least 10 % and long-term morbidity of at least 70%. It has been shown that the preponderance of kernicterus cases occurs in infants with high bilirubin (more than 20 mg/dl).[15] Reports from many countries show that kernicterus appears at TSB levels of > 25 mg/dl in healthy term infants. One study by Harris *et al*[16] evaluated breastfed neonates with bilirubin encephalopathy with a TSB level of > 25 mg/dl for period of two years and three months and reported that neurological disturbances were only temporary.

The prevention of bilirubin-induced brain injury is based on the detection of infants at risk for developing severe hyperbilirubinemia.[17] The outcome in our babies was good; the babies were managed according to the AAP guidelines such as performing assessment before discharge, performing follow-up and then carrying out intervention as soon as possible when it was needed. We also avoided unnecessary treatment.

In summary, we managed hyperbilirubinemic infants based on the AAP guidelines and the response was good. The babies were clinically well and the OAE results were normal. We think that these guidelines are safe to be applied in Indonesia, although further education for parents and further evaluation using the BERA examination is necessary at least when the child is able to talk.

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