Management of Hyperbilirubinemia in Newborn Infants 35 or More Weeks of Gestation: American Academy of Pediatrics, 2022

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Guidelines for management of hyperbilirubinemia in newborn babies 35 week or more have recently been updated by the American Academy of Pediatrics (AAP). This article compares the two guidelines (previous guidelines in 2004 and new guidelines) and lists the changes in diagnosis and management of hyperbilirubinemia proposed in the new guidelines along with implications for our setting.

Neonatal hyperbilirubinemia is a common problem faced by the pediatricians managing newborns. It is the seventh most common of cause of neonatal mortality in first 7 days of life worldwide and can lead to devastating long term sequelae including kernicterus spectrum disorder (KSD) [1]. American Academy of Pediatrics (AAP) recently revised their previous guidelines on management of hyperbilirubinemia in newborns born at or above 35 weeks of gestation [2,3]. These guidelines have been designed primarily for developed countries where disease profile is different and proper facilities for follow-up care are available. Infants in developing countries have different risk factors (prematurity, sepsis etc.), and facilities for prompt detection and treatment are sparse. Even so, AAP guidelines have been widely used and have been referred to in our national guidelines, primarily for defining treatment thresholds [4]. Given their routine use, it is important for pediatricians caring for neonates to be aware of the updated changes in these guidelines (**Table I**).

ASSESSMENT, MONITORING AND PREVENTION OF HYPERBILIRUBINEMIA

The new AAP guidelines 2022 re-emphasize the need for visual assessment of jaundice every 12 hours after birth and need to measure either transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) if jaundice is present in the first 24 hours of life. It is now recommended to measure bilirubin (TcB or TSB) in all babies between 24 to 48 hours of life as visual inspection is deemed far too inaccurate to assess the level of jaundice. Although TSB should be used as the definitive test to guide the need for phototherapy or exchange transfusion, TcB values are valid for screening the need for TSB estimation and decreasing need for sampling. TSB should be done if TcB value is within 3mg/dL of phototherapy threshold or ≥15 mg/dL. New guidelines also advise to consider the rate of rise of bilirubin if multiple values of TcB or TSB are available, terming rise of ≥0.3 mg/dL/h in first 24 hours and ≥0.2 mg/dL/h thereafter as exceptional, indicating hemolysis and need for direct antiglobulin test (DAT). The increased focus on objective measurement by either TSB or TcB makes it difficult to follow the guidelines strictly in LMICs. This is due to limited availability of TcB and even serum bilirubin estimation machines at primary and secondary health care settings where infants are first assessed for jaundice and where the visual inspection (guided by Kramer's chart) is relied upon for defining the need for testing [5].

Among the risk factors for neurotoxicity, asphyxia, lethargy, temperature instability and acidosis in the 2004 guidelines have been replaced by the term 'significant clinical instability' in the preceding 24 hours, thereby broadening the scope, depending on the clinical judgement. This along with sepsis, hypoalbuminemia (≤3 g/dL), hemolytic disease (including isoimmune, G6PD deficiency or other hemolytic conditions) and low gestation age (<38 weeks) are the hyperbilirubinemia neurotoxicity risk factors, thereby lowering the threshold for treatment.

New guidelines have reinforced the importance of providing support for breastfeeding and advice that oral supplementation with water or dextrose should not be given to prevent jaundice.

Blood group and DAT is recommended in all the babies born to Rh-negative mother whose antibody status is unknown; if positive, TSB is recommended 4

Table I Important Changes in 2022 Revision of American Academy of Pediatrics Guidelines on Hyperbilirubinemia

2004 Guidelines [2]	*2022 Guidelines [3]*
Antenatal maternal antibody screening	
Maternal screening recommended. No specific or detailed recommendations for interpretation of DAT following anti-Rh prophylaxis use in the mother.	Maternal screening for anti-erythrocyte antibodies in Rh-negative mothers, and if positive to test infant for blood group and DAT. A positive DAT may be ignored in cases when DAT is positive only for anti-Rh, and mother turned positive only following anti-Rh prophylaxis.
Screening for jaundice	
Universal screening by visual assessment every 8-12 h. TSB or TcB measurement, if jaundice appears in first 24 h or seems excessive.	Universal TSB or TcB screening is recommended between 24-48 h or prior to discharge if it occurs earlier.
Risk factors for significant hyperbilirubinemia	
–	Include lower gestational age, jaundice in the first 24 h, TSB/TcB nearing PT threshold or use of PT before discharge, hemolytic conditions, exclusive breastfed infant with suboptimal intake, scalp hematoma, and history of PT in parents or siblings. Additions: Down Syndrome Omissions: Maternal age, male gender and East Asian race.
Hyperbilirubinemia neurotoxicity risk factors	
Albumin <3g/dL, sepsis, isoimmune hemolytic disease, G6PD deficiency, acidosis, asphyxia, and significant lethargy.	Gestational age <38 wk, albumin <3 g/dL, sepsis, hemolytic conditions and significant clinical instability in previous 24 h.
Breastfeeding jaundice	
Formula or EBM supplementation recommended for breast fed infants receiving phototherapy, in case of excessive weight loss or dehydration.	Better described as Suboptimal intake hyperbilirubinemia. In infants with TSB nearing the PT threshold, with history suggestive of suboptimal feeding and excess weight loss, supplementation with formula can be considered.
Home-based PT for discharged newborns	
Home-based PT may be used for newborns with TSB 2-3 mg/dL below the PT threshold, and not to be used in any infant with risk factors.	Home-based PT recommended to be used for discharged newborns who meet the following criterion: Gestation ≥38 wk, age >48 h, adequately feeding, no risk factors for neurotoxicity, no previous phototherapy, TSB concentration no more than 1 mg/dL above the phototherapy treatment threshold, an LED-based phototherapy device available, TSB measured daily.
Discontinuation of PT	
No standard for discontinuation. PT may be discontinued when TSB falls below 13-14 mg/dL.	PT can be discontinued when TSB falls 2 mg/dL below the cut-off at which PT was initiated. Longer duration recommended for those with risk factors for rebound hyperbilirubinemia.
Rebound hyperbilirubinemia	
Risk factors: No particular risk factors listed.	Gestational age below 38 wk, PT initiation below 48 h, and hemolytic disease.
Timing of measurement: Within 24 h after discharge, if initiated early, discontinued before 3-4 d of life, and in a newborn with hemolytic disease.	On the day after PT is stopped (at least 12 h, preferably 24 h). Earlier measurement (at 6-12 h) for those with aforementioned risk factors.
Method: Not mentioned.	TcB can be used if at least 24 h have elapsed since stopping PT.
Escalation of care threshold	
Definition: No such threshold defined.	2 mg/dL below exchange threshold defined as "escalation of care" threshold.
IVIG recommended in isoimmune hemolytic disease TSB within 2-3 mg/dL of exchange threshold.	*Treatment/monitoring*: NICU admission, intravenous hydration and intensive PT.

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Table I *continued*

2004 Guidelines [2]	*2022 Guidelines [3]*
	Consider IVIG in isoimmune hemolytic disease. 2-hourly TSB monitoring to be done till it falls below the threshold.
	Workup: Measure total and direct bilirubin, albumin, blood chemistry, blood group, send for cross match to arrange blood for ET, CBC, and G6PD levels in all these infants.
Exchange transfusion (ET)	
For readmitted infants, ET considered only if TSB remained above exchange threshold after 6 h of intensive PT (except for those infants who presented with features of ABE).	Recommended for ABE or TSB at exchange cut-offs. Recommendations no longer vary for during birth hospitalization and readmissions in this regard.
Hematocrit of blood: Not specified	Recommend use of blood with 40% hematocrit for ET for the benefit of increasing bilirubin clearance with additional albumin.
Risk assessment before discharge and subsequent follow up	
Schedule based on Bhutani nomograms for risk stratification, based on pre-discharge bilirubin (TcB or TSB).	Schedule based on difference between pre-discharge TcB/TSB (measured at least 12 h after birth) and phototherapy cut-off.

ABE-acute bilirubin encephalopathy, CBC-complete blood count, DAT-direct antiglobulin test, EBM-expressed breast milk, ET-exchange transfusion, G6PD-glucose-6-phospphate dehydrogenase, IVIG-Intravenous Immunoglobulin, PT-phototherapy, TcB-transcutaneous bilirubin, TSB-total serum bilirubin.

hourly twice followed by 12 hourly, along with early initiation of phototherapy.

In case of prolonged jaundice persisting beyond 3-4 weeks in breastfed and 2 weeks in formula-fed babies, measurement of TSB with direct bilirubin is recommended, along with evaluation for hypothyroidism.

TREATMENT OF HYPERBILIRUBINEMIA

New guidelines have raised the threshold for initiation of phototherapy and exchange transfusion at all gestations, recognizing that bilirubin neurotoxicity occurs well beyond the threshold of 2004 guidelines [6]. While raising these thresholds, it is emphasized that these guidelines are applicable only to developed nations as they require strict monitoring and follow-up post discharge and thus may not be applicable if follow-up is uncertain, as is often the case in resource-limited settings. To mitigate the issue of uncertain follow-up in LMICs, some experts advocate a lower threshold for initiation of treatment in secondary care settings, while maintaining the same cut-offs in tertiary care settings given that the follow up is certain and regular [5].

In the new guidelines, hour-specific phototherapy and exchange transfusion thresholds have been provided for each week of gestation age from 35 to 40 weeks in the low-risk group and 35 to ≥38 weeks for babies with hyperbilirubinemia neurotoxicity risk factor group. New thresholds also consider the postmenstrual age of the neonate and suggest that TSB should be measured within 12 hours after starting phototherapy.

Discontinuation of phototherapy, which was earlier advised at TSB <13-14mg/dL, is now advised when TSB falls 2mg/dL below the threshold at which it was started. Further fall in TSB may be targeted if there is a substantial risk of rebound hyperbilirubinemia (as suggested by age <48 hours at start, gestational age <38 weeks or in setting of hemolytic disease) [7]. In these cases, it is also advised to measure TSB 6-12 hours after stopping phototherapy. In others, TSB is to be repeated the day after stopping phototherapy. TcB can replace TSB if used at least 24 hours after stopping phototherapy [8].

Major additions to these guidelines are statements about "escalation of care" when TSB approaches exchange transfusion (ET) threshold (defined as 2 mg/dL below ET threshold). Escalating care, described as a medical emergency, includes immediate admission to NICU with facility of ET, intensive phototherapy, intravenous hydration, blood tests for albumin, TSB, direct bilirubin, and arranging blood for ET. It is followed by TSB measurement at two-hourly intervals till TSB falls below escalation value.

Guidelines maintain previous stand of optional treatment with intravenous immunoglobulin (IVIG; 0.5-1g/kg)over 2 hours in patients with isoimmune hemolytic disease which can be repeated after 12 hours if they require escalation of care [9].

Any infants showing signs of advanced bilirubin encephalopathy (hypertonia, retrocollis, and apnea)

should receive ET irrespective of TSB. Blood with hematocrit of 40% is preferred for ET, with the rationale that it would provide additional albumin augmenting binding of bilirubin.

Post-discharge follow up is now based on the difference between TcB/TSB value at discharge and phototherapy threshold. Use of risk nomogram by Bhutani, et al. [10] for this purpose is no longer advised as they do not consider gestational age and risk factors.

IMPLICATIONS FOR PRACTICE

The actual impact of new thresholds on number of babies receiving phototherapy and exchange, and by extension, on the healthcare system, will become clear in future. Considering that the treatment threshold has been increased for all gestations, there is a probable potential to decrease the treatment requirement and the duration of hospital stay. However, there is an invigorated emphasis on monitoring and follow up, and a recommendation for rapid and timely escalation of care. This is aided by TcB machine facilitating rapid serial evaluation, which is still not readily available in our setting. Availability of TcB machines at delivery centers or alternative like smart phone applications or newer point of care serum bilirubin machines along with structured follow-up schedule is imperative for successful adoption of these guidelines. Individual centers will need to devise an effective machinery to provide optimal follow up services bearing in mind that increased treatment threshold carries a potential of devastating consequence of chronic bilirubin encephalopathy if follow up is inadequate. This can be done by making the follow up for jaundice an essential part of neonatal care and making the discharging unit responsible for follow up. Additionally, the risk factors including infection are also different in LMICs. The contribution of infections to severe jaundice or kernicterus has been reported to vary from 14% in Africa to 31% in Asia, compared with 2% in major HICs [11]. Delays in delivering effective treatments, routinely available in developed countries, continue to account for the high burden of neonatal hyperbilirubinemia in LMICs.

Besides evaluation, it is evident that treatment guidelines cannot be implemented in their entirety in our settings. Home phototherapy would not be feasible in most cases. Additionally, the recommendation to stop phototherapy only after TSB is 2 mg/dL below the initial phototherapy threshold is impractical to be applied in case of isoimmune hemolytic anemia, where the phototherapy may be initiated in the first few hours of life. Another example is the recommendation to use blood with hematocrit of 40% for ET. It will be interesting to see if there is an increase in the requirement of subsequent packed RBC transfusion in these babies. So, it is prudent that the experience and practical issues faced with the new guidelines are reported and recommendations more suitable to our setting can be formulated.

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