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Evaluation of Neonatal Hyperbilirubinemia: A New Hour-Specific Serum Bilirubin Nomogram for Neonates ≥ 35 Weeks of Gestation

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Abstract

Evaluation for hyperbilirubinemia is an integral part of newborn care. They anticipate that with concerted efforts by multiple investigative teams, neonatal bilirubin assessment and management programs will become more evidence-based, more effective, less expensive, more focused on neonates likely to benefit from phototherapy, and better able to prevent bilirubin-induced toxicities.

Keywords: Hyperbilirubinemia; Bilirubin; Nomogram; Neonates

Introduction

Evaluation for hyperbilirubinemia is an integral part of newborn care [1,2]. In 1999, Bhutani et al. [3] published an hour-specific bilirubin nomogram constructed from prehospital discharge Total Serum Bilirubin (TSB) values of 2840 neonates who had negative Direct Antiglobulin Tests (DAT). After defining hour-specific percentiles for TSB in newborns ≥ 35 weeks of gestation, the publication reported the ability of hour-specific predischarge serum bilirubin percentiles to predict subsequent hyperbilirubinemia. The prognostic value of hour-specific predischarge serum bilirubin percentiles was upheld in subsequent publications by the same group [4,5]. Therefore, the Bhutani et al. [3] publication was central to developing the 2004 and the 2009 American Academy of Pediatrics (AAP) clinical guidelines for managing hyperbilirubinemia in the newborn infant ≥ 35 weeks [6,7].

Neonatal Hyperbilirubinemia

Figure 1 the 2004 AAP guideline Phototherapy Chart (Hour Specific Nomograms for NNJ) for neonates 35 weeks or more with significant indirect Hyperbilirubinemia [6].

The Bhutani nomogram was widely used and impactful, in part because no other hour-specific serum bilirubin nomogram existed. Despite this, it was limited by a small sample size, and the data were not sufficiently robust to stratify by sex, or specific gestational ages between 35 and 40 weeks, or race. In addition, later publications recognized biases in the Bhutani study design. Specifically, the nomogram data were generated only from newborns who had at least one outpatient follow-up TSB (2976/13,003). Because obtaining an outpatient TSB was at the discretion of the outpatient clinician, this was likely a biased sample [8,9].

Since 2004, the Intermountain Healthcare hospitals have mandated 1 or more TSB determinations on each neonate during the birth hospitalization, with a report to the responsible clinician, including suggestions for management [10]. They used data from this program to recreate the Bhutani nomogram. To do this they excluded TSB values of neonates with a positive DAT, and (in keeping with our intermountain healthcare neonatal reference interval guidelines) [11]. They also excluded TSB values from neonates with an eventual diagnosis of the hemolytic disorders hereditary spherocytosis and Glucose-6-Phosphatase Dehydrogenase (G6PD) deficiency [12,13].

They aimed to develop a statistically rigorous, hour-specific bilirubin nomogram for newborns based on a very large data set; and use it prospectively as a replacement for the 1999 Bhutani nomogram.

Results

In a new report, they present an hour-specific bilirubin nomogram based on first predischarge serum bilirubin of 397,395 newborn infants, including analysis of the effect of sex, gestational age, and race (Table 1). The percentile curves generated from the data are shown in Figure 2. They had

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Table 1: The number of TSB values we used to construct the new bilirubin nomogram is shown, according to the subsets of gestational age at birth, sex, and maternally declared race/ethnicity.

Gestational age at birth (wk)		Sex		Race/ethnicity	
≥ 40	94272 (23.7)	Male	204017 (51.3%)	White	323906 (81.5%)
$39^{0/7}$-$39^{6/7}$	161070 (40.5%)	Female	193378 (48.7%)	Unknown or undeclared	38527 (9.7%)
$38^{0/7}$-$38^{6/7}$	77955 (19.6%)			Hispanic	55742 (14.0%)
$37^{0/7}$-$37^{6/7}$	39556 (10.0%)			Asian	5866 (1.5%)
$36^{0/7}$-$36^{6/7}$	16779 (4.2%)			Hawaiian or pacific Islander	4409 (1.1%)
$35^{0/7}$-$35^{6/7}$	7763 (1.96%)			Black	2868 (0.7%)
				American Indian or Alaska Native	1885 (0.5%)

For the race/ethnicity column, the sum of the percentage exceeds 100% because some subjects are counted in multiple categories, according to mother's medical record

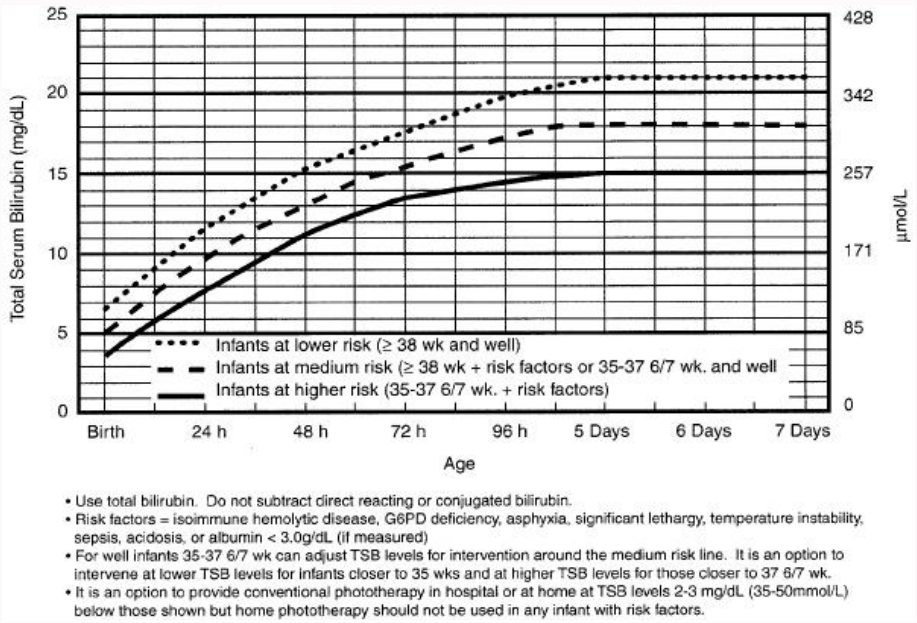

Figure 1: The 2004 AAP guideline phototherapy chart (Hour specific nomograms for NNJ) for neonates 35 weeks or more with significant indirect Hyperbilirubinemia.

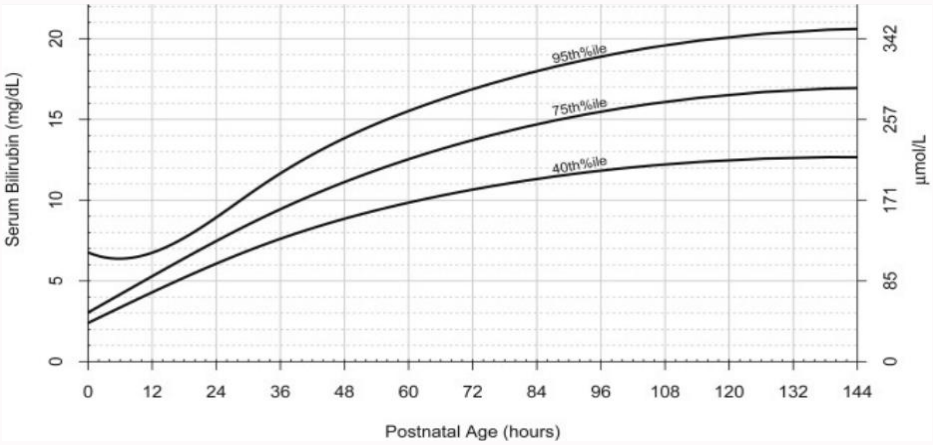

Figure 2: The new neonatal bilirubin nomogram.

sufficient data in the set to estimate the 40th, 75th, and 95th percentiles at all time points from birth to 144 postnatal hours. For comparison, they superimposed the 1999 Bhutani curves on their new curves (Figure 3). Curves for the 4 subgroup analyses are shown in Figure 4.

Regarding gestational age (panel A), starting at 36 h to 48 h, the younger gestational age neonates (35 to 36 weeks) had significantly higher 40th, 75th, and 95th percentile TSB values than did the more mature neonates (≥ 37 weeks; P<0.0001). The magnitude of this difference is constant through 96 h of life. After 96 h, the data available for earlier gestation group is sparse, thus, the comparison is truncated.

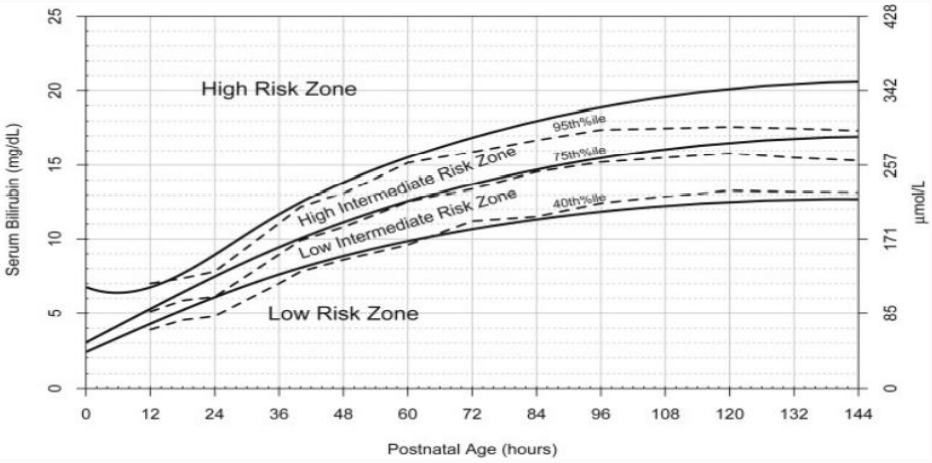

Figure 3: For comparison, they superimposed the 1999 Bhutani curves on their new curves.

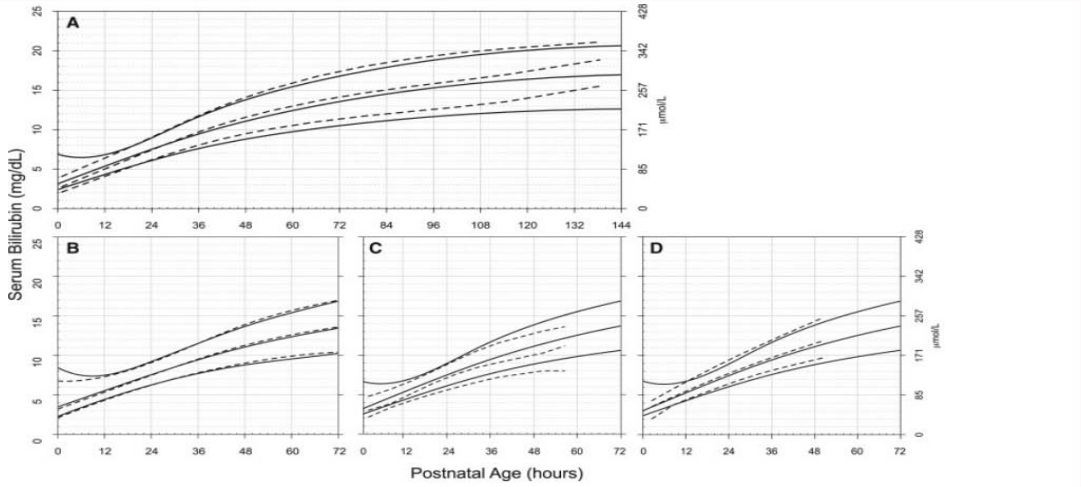

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Figure 4. The 40th, 75th, and 95th percentile curves for TSB by hour for population subgroups. **A,** Percentile curves for 24 958 neonates born between $35^{0/7}$ and $36^{6/7}$ weeks of gestation (*dashed lines*) are superimposed on curves for those born ≥37 weeks (*solid lines*; n = 372 437). **B,** Percentile curves for 204 017 male neonates (*dashed lines*) and 193 378 female neonates (*solid lines*) born at ≥35 weeks of gestation. **C,** Percentile curves for 2868 Black neonates (*dashed lines*) born at ≥35 weeks of gestation are superimposed on the analogous curves (solid lines) for the non-Black neonates born at ≥35 weeks of gestation (n = 394 527). **D,** Percentile curves for 5866 Asian neonates (*dashed lines*) born at ≥35 weeks of gestation are superimposed on the analogous curves (*solid lines*) for the non-Asian neonates born at ≥35 weeks of gestation (n = 391 529).

Figure 4: The 40th, 75th and 95th percentile curves for TSB by hour for population subgroups.

Regarding sex (panel B), we observed no significant differences in TSB percentiles between male and female neonates.

Regarding race (panel C), after 36 h the 40th, 75th, and 95th percentile TSB values for Black neonates are approximately 1 mg/dL lower than their peers.

Panel D shows that TSB values for Asian neonates are approximately 1 mg/dL higher than their peers. After 52 h, the data for these 2 race-based populations became too sparse for estimation.

A, GA, Percentile curves for 24,958 neonates born between 35 and 36 weeks of gestation (dashed lines) are superimposed on curves for those born ≥ 37 weeks (solid lines; n=372,437).

B, Sex, Percentile curves for 204,017 male neonates (dashed lines) and 193,378 female neonates (solid lines) born at ≥ 35 weeks of gestation.

C, Race, Percentile curves for 2,868 Black neonates (dashed lines) born at ≥ 35 weeks of gestation are superimposed on the analogous curves (solid lines) for the non-Black neonates born at ≥ 35 weeks of gestation (n=394,527).

D, Percentile curves for 5,866 Asian neonates (dashed lines) born at ≥ 35 weeks of gestation are superimposed on the analogous curves (solid lines) for the non-Asian neonates born at ≥ 35 weeks of gestation (n=391,529) [14].

Conclusion

They anticipate that with concerted efforts by multiple investigative teams, neonatal bilirubin assessment and management programs will become more evidence-based, more effective, less expensive, more

focused on neonates likely to benefit from phototherapy, and better able to prevent bilirubin-induced toxicities.

They believe that their new version of the Bhutani bilirubin nomogram is one step toward achieving those goals.

An updated and more informative Bhutani neonatal bilirubin nomogram, based on 140 times the number of subjects included the 1999 version, is now in place in their health care system.

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