Bilirubin Concentrations in Jaundiced Neonates with Conjunctival Icterus

Abeer Azzuqa, MD, and Jon F. Watchko, MD

Objectives To assess the total serum bilirubin (TSB) levels at which conjunctival icterus is observed in neonates of ≥34 weeks gestation during the first week of life.

Study design Two convenience samples of neonates were examined for conjunctival icterus within 4 hours of TSB measurements. A concurrent assessment of cephalopedal cutaneous icterus was performed and the TSB characterized using the Bhutani hour-specific risk zone nomogram.

Results Two hundred forty neonates were studied of which 76 had conjunctival icterus. Conjunctival icterus was always accompanied by cutaneous jaundice to at least the chest and more often than not a TSB >14.9 mg/dL (255 umol/L) consistently in the 76th%-95th% to >95th% range on the Bhutani nomogram. Only a few infants with TSB in the range of 10-14.9 mg/dL (171-255 umol/L) had conjunctival icterus.

Conclusions Conjunctival icterus was observed in a subset of jaundiced neonates and associated with elevated hour-specific TSB levels frequently >95th% on the Bhutani nomogram. Conjunctival icterus is a sign of clinically relevant hyperbilirubinemia that merits a TSB measurement and evaluation of the infant. *(J Pediatr 2015;167:840-4)*.

Jaundice is observed in up to 85% of neonates[1,2] most often as dermal icterus, which typically follows a cephalopedal progression as postnatal total serum bilirubin (TSB) levels rise.[3] Conjunctival icterus, often mischaracterized as scleral icterus,[4-6] is less commonly reported in newborns, and the TSB levels at which it is clinically evident in neonates is undocumented. Although some suggest conjunctival icterus in neonates is indicative of mild hyperbilirubinemia (6-8 mg/dL [103-137 umol/L])[7] coincident with the onset of facial jaundice[7,8] and others, including the American Academy of Pediatrics assert it is a sign of significant neonatal hyperbilirubinemia that merits clinical evaluation,[9-11] no data exist to support these claims. Even the classic cephalopedal advancement of jaundice description by Kramer[3] makes no mention of ocular findings and the eyes are notably closed in his homunculus of icterus zones.

Outside the neonatal period, however, icterus is often first noted in the eyes and then in the skin with increasing jaundice severity.[12] Indeed, in adults, conjunctival icterus may be an early sign of hyperbilirubinemia and is detectable more often than not at TSB levels of 2.5-4.0 mg/dL (43-68 umol/L),[12] concentrations in newborns that are considered low and at which even dermal icterus is infrequently seen.[1,3] Surprisingly, there are no published data on the relationship between TSB levels and conjunctival icterus in neonates. Therefore, we characterized the TSB levels at which conjunctival icterus was observed in term and late-preterm neonates of ≥34 weeks gestation during the first week of life.

Methods

We prospectively studied 2 convenience samples of term (≥$37^{0/7}$ weeks) and late-preterm ($34^{0/7}$-$36^{6/7}$ weeks) gestation neonates admitted to the University of Pittsburgh Medical Center's Magee-Women's Hospital and Children's Hospital of Pittsburgh neonatal intensive care units. During the first 7 days of life, neonates were screened for TSB ≥10 mg/dL (171 umol/L) by one of the investigators, and those with a TSB level <10 mg/dL (171 umol/L) were excluded from study because prior observations invariably demonstrated an absence of conjunctival icterus at such concentrations. Our goal was to narrowly focus on the TSB detection range for conjunctival icterus. For the first 120 neonates enrolled (cohort 1), clinical observations were made by 1 of 2 experienced neonatologists neither of whom was blinded to TSB. In the second 120 neonates enrolled (cohort 2), observations were made by 2 neonatologists or pediatric physician examiners independently, one of whom was blinded to the TSB level. The study was approved by the University of Pittsburgh Institutional Review Board with a waiver of consent.

Infants were examined within 4 hours of serum bilirubin (TSB and direct bilirubin) measurement that was part of routine care. Infants were examined in a well lit room with fluorescent lighting and prior to phototherapy in those infant's so treated. The clinical assessment included a determination of: (1) the presence or absence of conjunctival icterus; and (2) the distal most extent of cutaneous jaundice as defined by dermal zones 1-5 using the Kramer[3] homunculus (0 = none; 1 = face and neck only; 2 = chest and back; 3 = abdomen below umbilicus to

TcB	Transcutaneous bilirubin
TSB	Total serum bilirubin

From the Division of Newborn Medicine, Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA

J.W. provides expert testimony in legal cases related to neonatal jaundice. A.A. declares no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.06.065

knees; 4 = arms and legs below knees; 5 = hands and feet). Dermal blanching with gentle thumb pressure was used to determine the extent of cutaneous jaundice. Examiners blinded to the TSB were instructed to assess the conjunctiva only and report their findings as icterus present or absent.

The TSB level was categorized into 1 of 4 hour-specific bilirubin risk zone percentiles (<40th, 40th-75th, 76th-95th, >95th) using the Bhutani nomogram.[13] The infants medical record was reviewed for the following: (1) birth weight; (2) sex; (3) gestational age; (4) mode of feeding; (5) hour of postnatal life of the TSB ≥ 10 mg/dL; (6) maternal blood type and antibody screen; (7) infant blood type and direct Coombs test (if measured); and (8) ethnicity (maternal self-report).

Data from each cohort were analyzed as a function of the presence or absence of conjunctival icterus using standard descriptive statistics, unpaired *t* tests, χ^2, and Mann-Whitney U test as appropriate. The McNemar test was used to assess the effect of examiner blinding status on the detection of conjunctival icterus in cohort 2. The positive and negative predictive values of conjunctival icterus in relation to >95% on hour-specific Bhutani bilirubin nomogram were determined.

Results

The distribution of individual neonates as a function of TSB and conjunctival icterus status for cohort 1 and 2 is shown in Figure 1; their respective demographic and summary data are reported in Tables I and II. As the paired examinations for the presence or absence of conjunctival icterus in cohort 2 were largely concordant (90.8%) and there was no statistical association between examiner blinding status and the detection of conjunctival icterus (OR 1.20; 95% CI 0.31-5.0; McNemar test), the concordant blinded and nonblinded observations were combined in the summary of cohort 2 (Table II). Discordant observations are also detailed in Table II.

A total of 76 neonates had conjunctival icterus (cohort 1: n = 34; cohort 2 concordant: n = 31; cohort 2 discordant: n = 11); 43 (57%) during the birth hospitalization and 33 (43%) at the time of hospital re-admission for hyperbilirubinemia.

In both cohorts, conjunctival icterus was always accompanied by cutaneous jaundice whose cephalopedal extent ranged from zone 2 (chest and back) to 5 (hands and feet) on the Kramer scale (Tables I and II). No infant with

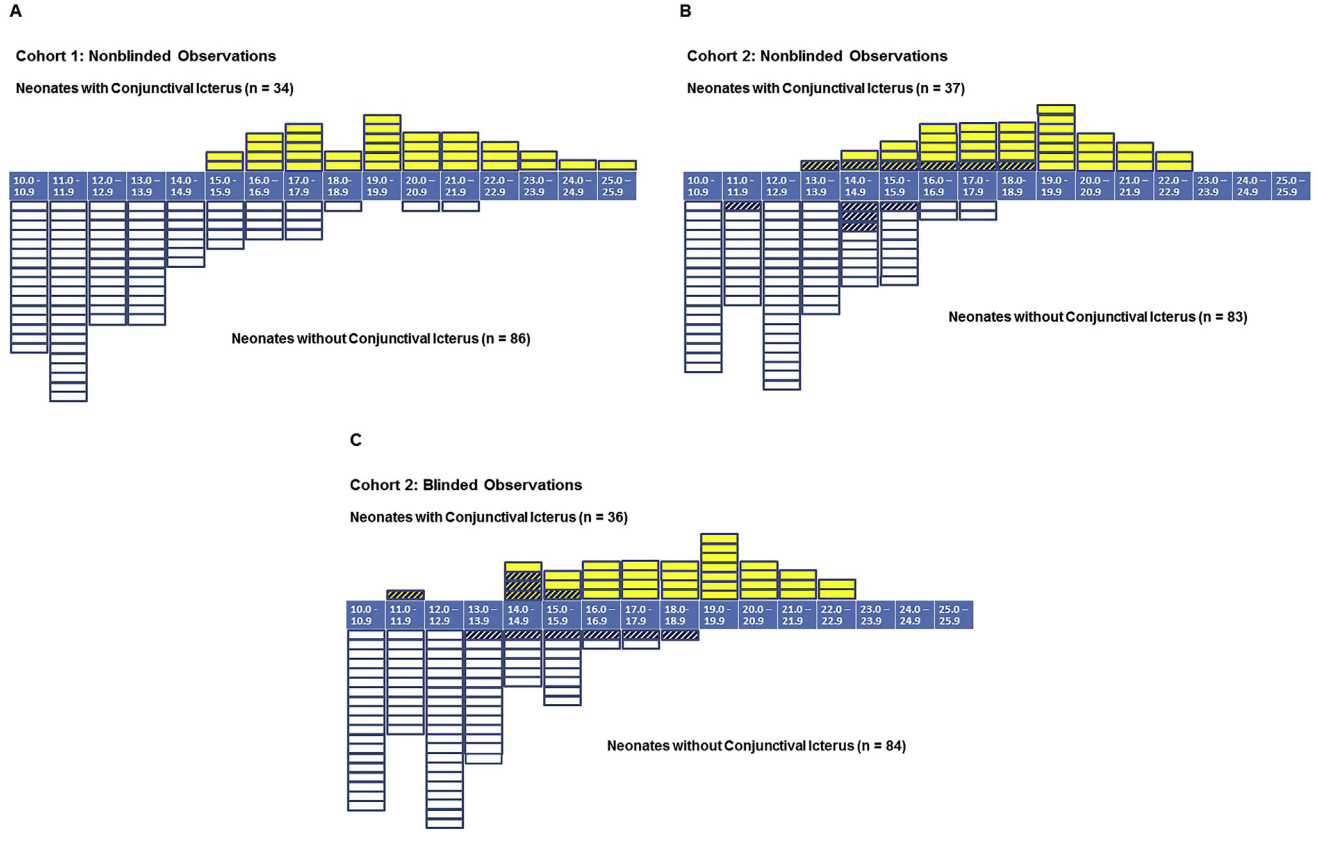

Figure 1. Plot of individual neonates (*each block = 1 subject*) as function of TSB and presence (*top*) or absence (*bottom*) of conjunctival icterus. **A,** Cohort 1; **B,** nonblinded observations from cohort 2; and **C,** blinded observations from cohort 2. The 11 discordant examinations in cohort 2 are indicated by hatched bars.