

The Natural History of Jaundice in Predominantly Breastfed Infants



WHAT'S KNOWN ON THIS SUBJECT: Newborn infants who are predominantly breastfed are much more likely to develop prolonged hyperbilirubinemia than those fed formula, but the prevalence of prolonged hyperbilirubinemia in a largely white, North American, breastfed population is unknown.



WHAT THIS STUDY ADDS: Practitioners can be reassured that it is normal for 20% to 30% of predominantly breastfed infants to be jaundiced at age 3 to 4 weeks and for 30% to 40% of these infants to have bilirubin levels ≥ 5 mg/dL.

abstract

FREE

BACKGROUND AND OBJECTIVES: Breastfed newborns are more likely to develop prolonged hyperbilirubinemia than those fed formula, but the prevalence of prolonged hyperbilirubinemia in a largely white, North American breastfed population is unknown. In this population, we documented the natural history of jaundice and the prevalence of prolonged hyperbilirubinemia, and we evaluated the utility of assessing the cephalocaudal progression of jaundice in office-based practices.

METHODS: We measured transcutaneous bilirubin (TcB) levels during the first month in 1044 predominantly breastfed infants ≥ 35 weeks of gestation and assigned a cephalocaudal zone score to each infant at the time of the TcB measurement.

RESULTS: TcB level was ≥ 5 mg/dL in 43% of infants at age 21 ± 3 days and 34% were clinically jaundiced. At 28 ± 3 days, the TcB was ≥ 5 mg/dL in 34% and 21% were jaundiced. There was a strong correlation between the TcB level and the jaundice zone score, but there was a wide range of TcB levels associated with each score.

CONCLUSIONS: Practitioners can be reassured that it is normal for 20% to 30% of predominantly breastfed newborns to be jaundiced at age 3 to 4 weeks and for 30% to 40% of these infants to have bilirubin levels ≥ 5 mg/dL. The jaundice zone score does not provide an accurate assessment of the bilirubin level, but a score of zero (complete absence of jaundice) suggests that the level is unlikely to be >12.9 mg/dL, whereas a score of ≥ 4 usually predicts a level of ≥ 10 mg/dL. *Pediatrics* 2014;134:e340–e345

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KEY WORDS

newborn jaundice, breastfeeding, prolonged jaundice, natural history, cephalocaudal progression

ABBREVIATIONS

CI—confidence interval
JZS—jaundice zone score
TcB—transcutaneous bilirubin
TSB—total serum bilirubin

Dr Maisels conceptualized and designed the study, drafted the initial manuscript, and revised the manuscript critically for important intellectual content. Drs Clune, Coleman, Gendelman, Kendall, McManus, and Smyth participated in the conceptualization and design; they, or their delegates, examined all of the patients and supervised the collection of data at each site; and they reviewed the article for important intellectual content. All authors approved the final manuscript as submitted.

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The association between breastfeeding and jaundice is well-known and well-documented,¹ as is the observation that breastfed infants are much more likely than formula fed infants to have jaundice that persists for several weeks or months after the infant's birth.^{1–6} Investigators in Turkey⁵ and Taiwan⁶ found that, at 4 weeks, some 20% to 28% of exclusively breastfed infants had total serum bilirubin (TSB) levels ≥ 5 mg/dL, but no similar data exist for infants in the United States. The cephalocaudal progression of jaundice is also well documented,^{7–11} as is the use of a score to document this progression,^{7,10,12} but the utility of this score in documenting a range of possible TSB levels, or as a predictor of subsequent hyperbilirubinemia, has been evaluated only in hospitalized newborns and not in infants seen in office practice.

Our objective was to document the natural history of jaundice in the first month in a predominantly breastfed, white population of newborns, to identify the prevalence of prolonged hyperbilirubinemia and the clinical observation of jaundice in these infants, and to evaluate the utility of the cephalocaudal zone score as a screen for hyperbilirubinemia in office-based pediatric practice.

METHODS

From September 2010 to August 2013 we obtained a convenience sample of 1732 transcutaneous bilirubin (TcB) measurements on 1044 predominantly breastfed infants ≥ 35 weeks of gestation. Some infants seen at follow-up had repeated TcB measurements at several visits. These infants were cared for in well-infant nurseries in southeast Michigan and followed in 5 pediatric office practices and the well-infant clinic of the Beaumont Children's Hospital. We used the Konica Minolta Dräger Air Shields JM-103 transcutaneous jaundice meter (Dräger Medical, Telford, PA)

to measure the TcB. Three TcB measurements were obtained from the midsternum and averaged. In our previous study of a mixed race population with 41% nonwhite infants,¹³ TcB measurements correlated well with TSB ($r = 0.913$) and measurements from the sternum correlated better with TSB measurements than TcB measurements from the forehead. Although we normally use the highest of these 3 measurements when screening newborns for hyperbilirubinemia, for the purpose of this study the 3 measurements were averaged and all TcB data are presented as the average of 3 measurements. Operational electronic checks were performed daily as recommended by the manufacturer to confirm that the light output was within range for both long and short wavelengths of light.¹⁴ If the readings were outside of the range, the instrument was returned for recalibration.

We defined “predominantly breastfed infants” as infants who received no more than 1 formula feeding per day. All data recorded from days 3 to 28 come from infants who were outpatients. To obtain data that represent the natural history of bilirubinemia in our study population, we also recorded the TcB levels in 108 hospitalized, exclusively breastfed infants in the first 2 days after birth. TcB measurements are obtained daily on all infants in our nursery and are also obtained routinely at follow-up office visits in each of the participating office practices and the hospital well-infant clinic. Office-based pediatricians and their nursing staff were trained in the use of the Kramer scale homunculus⁷ (Fig 1) and the JM-103. At each office visit, the pediatrician assigned a Kramer cephalocaudal score (hereinafter referred to as the “jaundice zone score” or JZS), and TcB levels were obtained by the office nurse, but the TcB measurement was not available to the pediatrician at

the time the jaundice zone was scored. Jaundice was considered to be present if the JZS was ≥ 1 (Fig 1).

The study was approved by the hospital Human Investigation Committee, which waived the need for consent, but parents were provided with written information about the study and could choose not to participate.

RESULTS

Demographic data are shown in Table 1 and results in Table 2 and Figs 2 and 3. At 21 ± 3 days, 20 of 59 infants (34%; 95% confidence interval [CI]: 25%–45%) were jaundiced (JZS ≥ 1), and 33 of 75 (44%; 95% CI: 33%–55%) had TcB levels ≥ 5 mg/dL. At 28 ± 3 days, 20 of 94 (21%; 95% CI: 14%–31%) were jaundiced, and the TcB was ≥ 5 mg/dL in 36 of 106 (34%; 95% CI: 26%–43%). (The denominators for the presence of jaundice are less than the number of infants seen because some infants did not receive a JZS.) There was a strong correlation between the mean TcB level and the JZS (Fig 3; $r = 0.722$, $P = .0000$) and the correlation was equally strong at 14, 21, and 28 days and in nonwhite infants ($P = .0000$ in each case), but there was a wide range of TcB levels associated with each grade. Nevertheless, in 525 infants with a JZS of zero, the TcB was >12.9 mg/dL in only 4 (0.8%; 95% CI: 0.2%–1.9%) with a range of 13.0 to 15.5 mg/dL and >15 mg/dL in 1 (0.2%; 95% CI: 0.01%–1.2%). Forty-three infants had a JZS of 4 or 5. Only one of these infants (2.3%; 95% CI: 0.01%–13.2%) had a TcB <10 mg/dL. All TSB measurements included a direct bilirubin measurement and no infant had an elevated direct bilirubin.

DISCUSSION

Prolonged Jaundice in the Breastfed Infant

Pediatricians and family physicians, with some regularity, see thriving breastfed

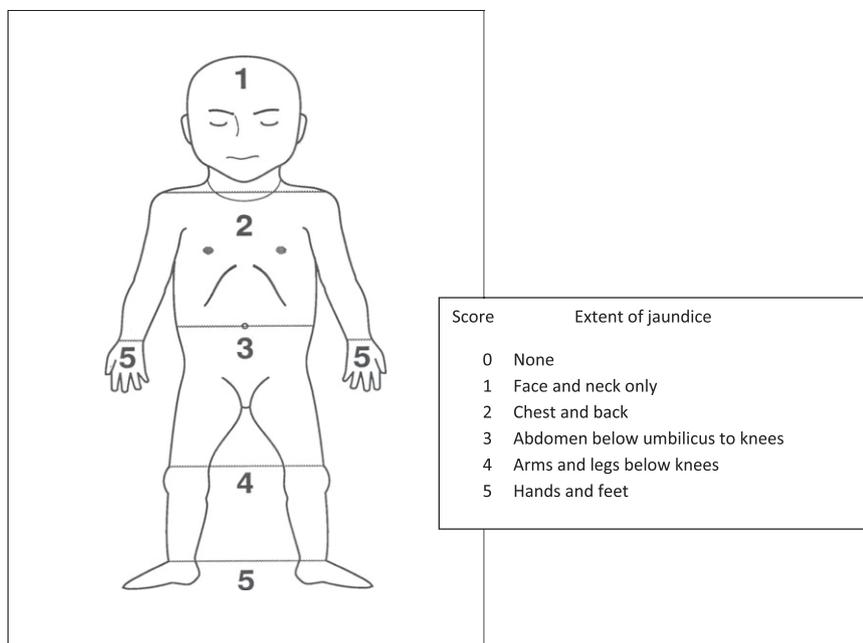


FIGURE 1
Homunculus used to assign JZS.

infants who are still jaundiced at ages 3 to 4 weeks and sometimes beyond but, to date, there are limited published data on how often this phenomenon occurs. In Fig 2, we provide the first documentation, with percentiles, of the natural history of bilirubinemia in a large population of healthy, breastfeeding newborns up to age 28 ± 3 days. Kivlahan et al² documented the natural history of jaundice with mean TcB index measurements (the instrument used did not provide a bilirubin measurement) in 115 white and 25 African American infants for the first 21 days. The data did

not include percentiles or the proportion of infants with an elevated TSB or observed jaundice. We could identify only 2 studies in which a population of breastfed infants was followed for at least 4 weeks and in whom TSB levels were measured in all infants. Chang et al⁶ followed 125 Chinese breastfed infants (≥ 37 weeks) and found that 28% had a TSB > 5.9 mg/dL beyond age 28 days. Tiker et al⁵ followed 282 breastfed, term Turkish infants. At 1 month, 57 (20%) had TSB levels > 5 mg/dL and 17 (6%) > 10 mg/dL. To date, there are no satisfactory data documenting the prevalence of elevated bilirubin levels or observed jaundice in a population of predominantly white, breastfed infants. Although, in our study, some 34% of infants at age 28 ± 3 days had TcB levels ≥ 5 mg/dL, on clinical observation alone (a JZS of ≥ 1), only 24% of these infants appeared jaundiced to an experienced observer.

Several mechanisms have been proposed to explain why breastfed infants are more likely to be jaundiced in the first 7 to 10 days than those fed formula, but

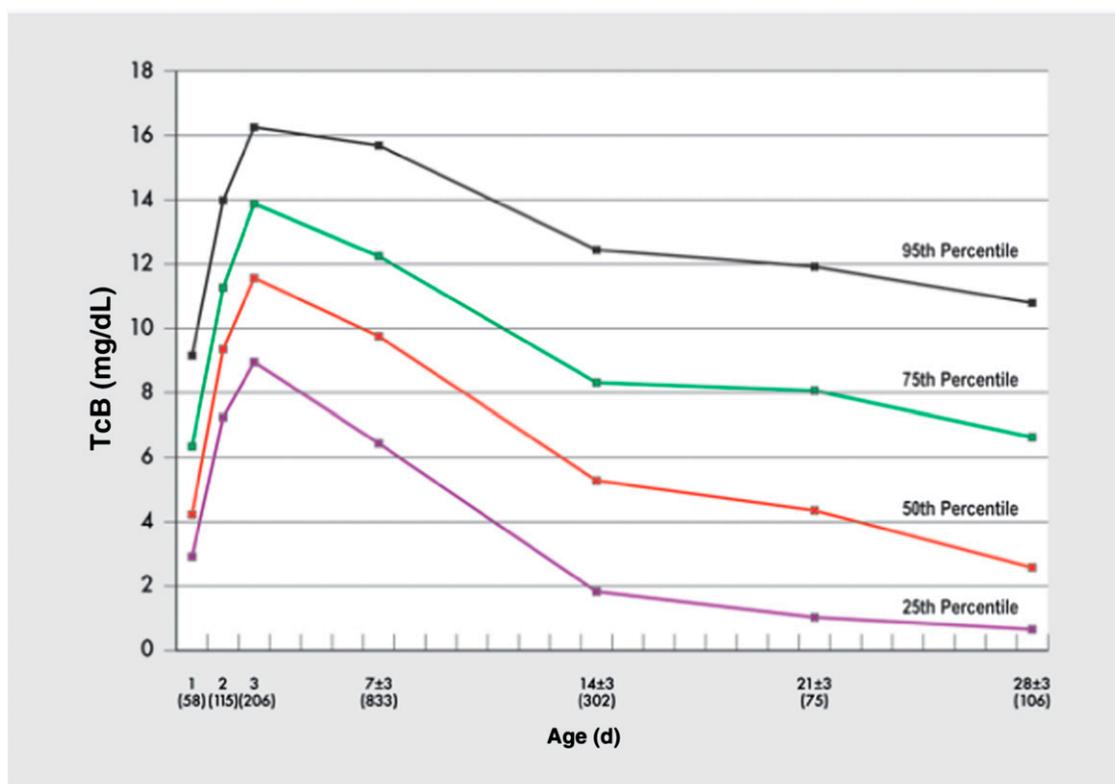
an explanation for why breastfed infants are more likely to have prolonged jaundice has been elusive. The first suggested mechanism for this phenomenon came from the studies of Arias and Gartner¹⁵ who identified a progestational steroid, pregnane-3(α), 20(β)-diol in the milk of mothers whose infants had prolonged hyperbilirubinemia. This steroid was shown to inhibit bilirubin conjugation in vitro and was capable of producing hyperbilirubinemia when administered to 2 healthy newborns,¹⁶ but subsequent studies could not confirm these findings.^{17–19} The contemporary era of genetic diagnosis, however, has cast a new and fascinating light on the causes of unexplained hyperbilirubinemia^{20,21} and prolonged breast milk jaundice is now a condition for which in some infants, and perhaps the majority,^{6,22,23} there is a clear genetic pathogenesis characterized by polymorphisms of the *UGT1A1* gene.^{22,24} This is the gene that determines the structure of the isoenzyme, uridine diphosphate glucuronosyl transferase 1A1 (*UGT1A1*), that is responsible for bilirubin conjugation. There is a well-documented association between prolonged breast milk jaundice and expression of the *UGT1A1* promoter variant, *UGT1A1*28*,²² that is the cause of Gilbert syndrome in white infants, and the *UGT1A1* coding sequence variant, *UGT1A1*6*, that causes Gilbert syndrome in East Asians.²⁴ In Gilbert syndrome, the monoconjugated bilirubin fraction predominates over the diconjugated fraction²⁵ and this enhances the enterohepatic circulation of bilirubin because hydrolysis of the monoglucuronide back to unconjugated bilirubin occurs at rates 4 to 6 times that of the diglucuronide.²⁶ Furthermore, it has now been demonstrated, that in the presence of the *UGT1A1*6* polymorphic mutation of *UGT1A1*, the addition of pregnane-3(α), 20(β)-diol will inhibit conjugation. This mechanism could therefore explain prolonged breast milk jaundice in some

TABLE 1 Study Population Demographics

Characteristics	N	%
Boy	526	50.4
Girl	506	48.5
Unknown	12	1.10
Race		
White	797	76.3
African American	75	7.20
East Asian	45	4.30
Other/mixed	22	2.10
Unknown	105	10.1
Gestation, wk		
< 37	54	5.20
37–42	945	90.5
Unknown	45	4.30

TABLE 2 TcB Bilirubin Levels

Age, d	1	2	3	7 ± 3	14 ± 3	21 ± 3	28 ± 3
<i>N</i>	58	115	208	841	306	75	106
TcB mg/dL, mean ± SD (range)	4.7 ± 2.7 (0–13.3)	9.2 ± 3.2 (0–18.3)	11.1 ± 3.8 (0–19.4)	9.1 ± 4.4 (0–18.6)	5.4 ± 4.0 (0–16.5)	4.9 ± 4.2 (0–16.7)	3.8 ± 3.7 (0–13.1)
TcB ≥5.0 mg/dL (%)	22 (38)	107 (93)	196 (94)	685 (81)	158 (52)	33 (43)	36 (34)
TcB ≥7.5 mg/dL (%)	7 (12)	84 (73)	174 (83)	585 (70)	101 (33)	24 (32)	18 (17)
TcB ≥10 mg/dL (%)	3 (5)	50 (43)	142 (68)	404 (48)	41 (13)	13 (17)	10 (9)
TcB ≥12.9 mg/dL (%)	1 (2)	13 (11)	77 (37)	158 (19)	12 (2)	1 (1)	1 (0.9)

**FIGURE 2**

TcB percentiles at each age. Numbers in parentheses are the number of measurements obtained at each age.

Asian infants.²⁷ Perhaps there is a similar additive role for pregnane-3(α), 20(β)-diol in breast milk and Gilbert syndrome in white infants.

Cephalocaudal Progression

As illustrated in Fig 3, although there is a strong correlation between the TcB level and the JZS,^{10,28} there is a wide range of TcB levels associated with each grade^{10,29,30} so that it is not possible to provide an accurate visual estimate of a bilirubin level. Nevertheless, this does not completely negate the value of the JZS. In a mixed racial

population of term and late preterm infants, Keren et al¹⁰ found that if the JZS was 0 (complete absence of jaundice), there was a 99% probability that significant hyperbilirubinemia would not develop. In our population, if the JZS was 0, 99.2% of infants had a TSB level \leq 12.9 mg/dL. Thus, if a 4- or 5-day-old infant is examined in good light, and no jaundice seen, it is reasonable to rely on clinical judgment regarding the need for a TSB level and subsequent follow-up, but the same cannot be said for a newborn before discharge. Because TSB levels that call for additional

evaluation or intervention are low in the first 36 to 48 hours, the range of values that corresponds to a JZS of 0 (Fig 3) is simply too wide to allow appropriate follow-up decisions to be made.³¹ A JZS of 2 to 5 at any age suggests the need for a TcB or TSB measurement to determine if additional investigation or intervention is necessary.

The pathogenesis of the cephalocaudal progression of jaundice has never been fully explained. Purcell and Beeby³² measured the TcB, skin temperature, and capillary refill time at the forehead,

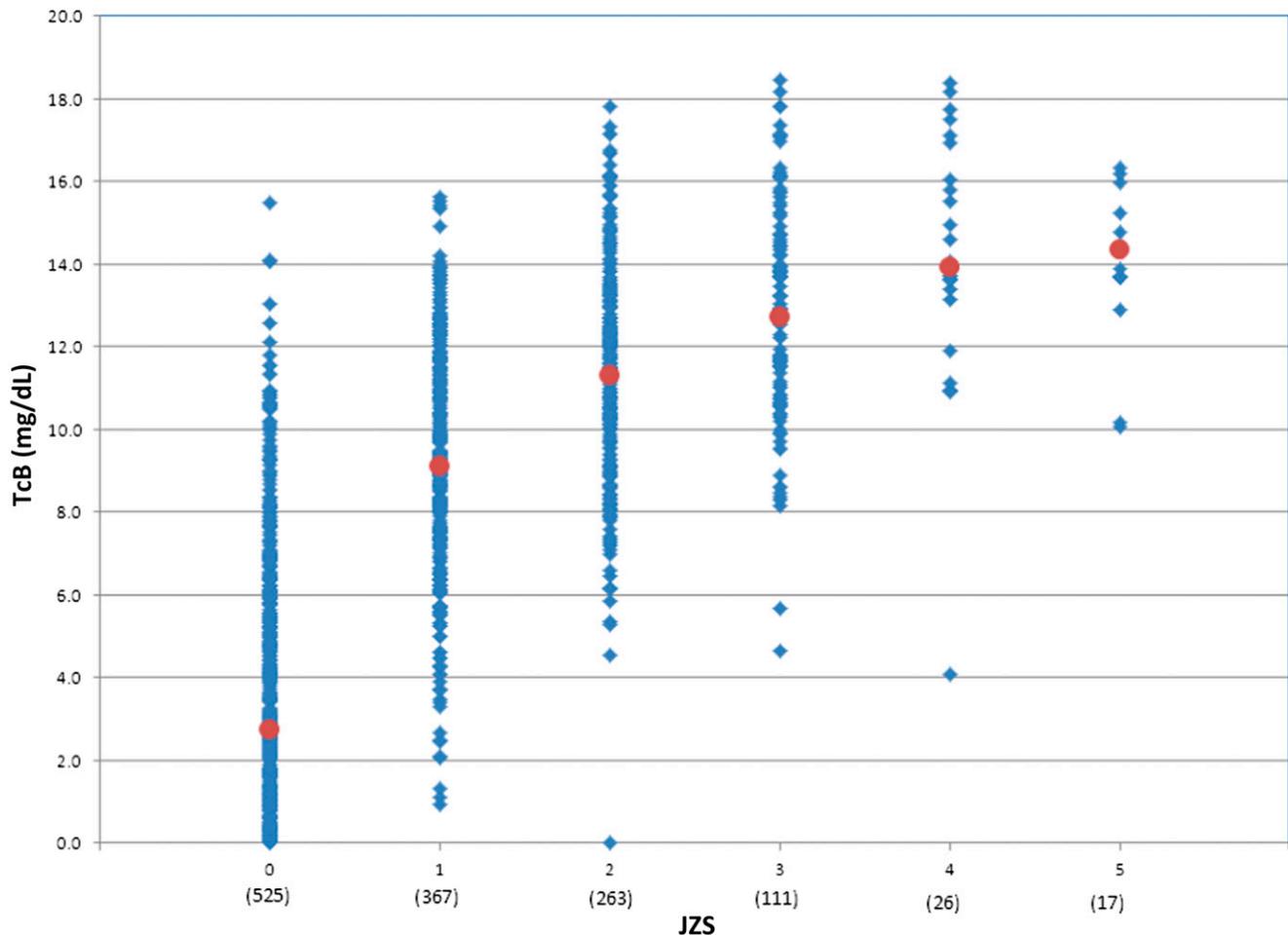


FIGURE 3 TcB levels corresponding to each JZS. Bold dots are median values. Numbers in parentheses are the number of infants in each zone. There is a strong correlation between the JZSs and the TcB measurements (linear regression $y = 2.9398x + 4.6778$, $r = 0.722$, $P = .0000$).

sternum, lower abdomen, midhigh, and sole of the foot. They observed a similar cephalocaudal progression of decreasing TcB and skin temperature and increasing capillary refill time, suggesting that the cephalocaudal progression of jaundice is a consequence of better perfusion of the head and proximal parts of the body and diminished capillary blood flow in distal parts. Nevertheless, we found that at 7, 14, 21, and 28 days, there was still a strong correlation between the JZS and the TcB. We would anticipate that by 14 days, at least, peripheral perfusion should be normal although this has not been measured.

Most recently, Azzuqa and Watchko³⁵ remind us to look at the eyes of jaun-

diced newborns. In their preliminary study, every one of 21 infants who had scleral icterus had a TSB >15 mg/dL (range, 15.3–24 mg/dL). If confirmed, this should be a useful sign for identifying infants with significant hyperbilirubinemia.

CONCLUSIONS

We provide the first data on the natural history of bilirubinemia in a population of predominantly breastfed, mainly white infants, for the first month after birth. The knowledge that, at 1 month, ~1:3 infants has a TcB ≥ 5 mg/dL and ~1:5 appears jaundiced, should be of practical value to practitioners who care for newborns and reassuring to the parents of infants who are still

jaundiced at age 4 weeks. We also show that there is a strong relationship between the cephalocaudal JZS and rising bilirubin levels and that this relationship persists up to age 28 days. Although the range of values within each zone is too large to allow an accurate determination of the actual bilirubin value, a score of 0 is highly predictive of a TcB value of <12.9 mg/dL, and a score of ≥ 4 will usually predict a TcB of ≥ 10 mg/dL.

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