Review Article



# Narrative review of the epidemiology of neonatal jaundice

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**Background and Objective:** Neonatal jaundice (NJ) is one of the most common causes for medical intervention in the newborn period. While transitory hyperbilirubinemia (HB) is present in almost all newborns, detection of jaundice requires a trained observer and good lighting.

**Methods:** PubMed and personal archives were searched during the period October-December 2020 for 'jaundice, neonatal' in combination with relevant key words, such as 'measurement', 'season', 'ethnicity', 'geograpy', 'birth weight', 'genetics OR family', 'sex OR gender', 'prematurity', 'nutrition', 'blood group incompatibility', 'infection', 'labor OR delivery'. 'Kernicterus' and 'bilriubin encephalopathy' were used as separate key words. Inclusion criteria were: publications dealing with jaundice human neonates and published in any of the Western European languages, publications in other languages or not dealing with humans were excluded.

**Key Content and Findings:** Thus, jaundice in the newborn has a reported incidence between 60% to more than 90%. Bilirubin, the molecule that causes the color of jaundice, is the end product of disassembly of heme-containing molecules, primarily hemoglobin. Therefore, conditions that increase hemolysis will increase bilirubin production and cause jaundice. Common conditions in the newborn are blood group incompatibilities and congenital hemolytic anemias. A family history of NJ increases the likelihood of jaundice in the present newborn, and is one of several examples of genetic conditions that contribute. Endocrine and metabolic conditions contribute, the most common being maternal diabetes. An increased incidence is seen in infants of Southeast Asian mothers, while African infants have a lower incidence unless they suffer from G-6-PD-deficiency. Drugs taken by the mother during pregnancy may impact on hepatic metabolism of bilirubin in the newborn, often by reducing the incidence of jaundice, and the same may happen with certain drugs given to the newborn. Birth trauma, through extravasation of blood, will increase bilirubin production and jaundice. Preterm infants have immature bilirubin metabolism and a higher incidence of jaundice. Breast-fed infants have an increased incidence of jaundice, which may also last longer.

**Conclusions:** Extreme NJ, associated with risk of kernicterus spectrum syndrome, has an estimated worldwide incidence of 99/100,000 or more, thus affecting 130,000 or more infants each year and calling for increased vigilance and preparedness for rapid therapeutic intervention.

**Keywords:** Neonatal jaundice (NJ); neonatal hyperbilirubinemia (HB); bilirubin; epidemiology

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## Introduction

Jaundice in the skin and/or conjunctiva of newborn infants [neonatal jaundice (NJ)] results when unconjugated bilirubin accumulates to a level that makes the yellow color visible to our eyes. Hyperbilirubinemia (HB), on the other hand, denotes a level of total serum bilirubin (TSB) which exceeds the normal range for healthy humans. Because our lab methods are more sensitive than our eyes, HB is usually present before we perceive this as NJ. The lowest TSB level at which NJ can be visually detected in neonates, is around 46–68 μmol/L (2.7–4.0 mg/dL) (1-3), though in older data

the range of detectability was as wide as 30–200 µmol/L (4). Infants with TSB levels at the lower end of these ranges may not be perceived as jaundiced by visual examination (3,4). Indeed, in Davidson *et al.*'s study from 1941 the TSB value above which >50% of infants were perceived to be jaundiced was around 70–85 µmol/L (4–5 mg/dL) (4). Our ability to detect NJ depends on the strength and color of the light we use for examination (5), the pigmentation of the infant's skin (5), pH and albumin levels in the infant (6), and on the individual who performs the examination, including her/his training and experience (7-9). Thus, it is not surprising that data on the incidence of NJ vary between studies.

The reference interval for normal TSB values in adults is defined based on a range of test results that encompass 95% of a healthy population, and is ~5–25 µmol/L (0.3–1.45 g/dL) (10). Therefore, in adults HB strictly speaking is any TSB value above this range. It is less clear how we should define HB in newborn infants, as most newborn infants have maximum TSB values that (I) exceed the normal adult range, (II) increase significantly during the first hours and days of life, and (III) in some cases may continue to be elevated for weeks and even months after birth (11). Bhutani *et al.* proposed the following definitions for severity of HB: 'significant': ≥291 µmol/L (≥17 mg/dL); 'severe': ≥342 µmol/L (≥20 mg/dL); 'extreme': ≥427 µmol/L (≥25 mg/dL); and 'hazardous': ≥513 µmol/L (≥30 mg/dL) (12). Maisels defined 'severe' in the same way as Bhutani *et al.*, but subsumed the 'hazardous' category from the latter under the label 'extreme' (13). Maisels also suggested that HB in neonates be defined as TSB levels that exceed the 95$^{th}$ percentile for the infant's age in hours for a given population (13). However, data on the 95$^{th}$ percentile for TSB relative to postnatal age in hours do not appear to be available for most populations, making the application of this proposal challenging. While reviewing the literature for the present paper, it became apparent that the terms NJ *vs.* neonatal HB have been used interchangeably (1,4,7,8,14-30) and variably (31-45). Herein I will use the term NJ to denote jaundice in the newborn identified by visual identification. I will use the term HB for any elevation of bilirubin values beyond the normal range for adults, whether identified by TSB or transcutaneous measurement (TcB), recognizing that neither TSB nor TcB measurements are precise, and that concurrent measurements using both methods often yield discrepant results (46). I will use the terms 'severe' HB, 'extreme', and 'hazardous' HB as defined by Bhutani *et al.* (12), recently also used by Olusanya *et al.* (47). Other definitions have also been used (32,48,49).

## Methods

PubMed and the author's personal archives were searched during the period October-December 2020 with the following search terms: jaundice, neonatal; jaundice, neonatal and epidemiology; jaundice, neonatal and lab methods; jaundice, neonatal and measurement; jaundice, neonatal and season; jaundice, neonatal and ethnicity; jaundice, neonatal and geography; jaundice, neonatal and birth weight; jaundice, neonatal and [genetics or family]; jaundice, neonatal and maternal age; jaundice, neonatal and maternal illness; jaundice, neonatal and prematurity; jaundice, neonatal and birth weight; jaundice, neonatal and [sex or gender]; jaundice, neonatal and nutrition; jaundice, neonatal and blood group incompatibility; jaundice, neonatal and infection; jaundice, neonatal and [labor or delivery]; kernicterus; bilirubin encephalopathy, only studies in human infants and published in western European languages were included, while non-human studies and *in vitro* studies published in other languages were excluded. This is a single author review, and publications were selected if the abstract showed that themes relevant to the overarching theme of this review were discussed therein, and also if the publication provided historical background for the development of our understanding of the epidemiology of neonatal jaundice. For this reason, strict modern criteria for population size or study design were not applied.

## The incidence of NJ *vs.* neonatal HB

Early in the 20$^{th}$ century Hirsch studied the relationship between clinical jaundice and serum bilirubin, the latter quantitated by an early version of the diazo reaction (50). She observed 100 infants daily during the first 5 days of life, and found that 80 of them had some degree of NJ during this period. She further noted that there was a relationship between her serum bilirubin measurements and the presence of NJ, however this claim does not seem to be based on any mathematical or statistical calculations (50).

Davidson and collaborators examined 99 infants daily for NJ during the first days of life under daylight conditions, using a tongue depressor to squeeze blood from the skin of the forehead and chin, and from the mucous membrane of the lower jaw (4). NJ was recorded as present on a least 1 occasion in 63 infants, i.e., 64%. In 16 of these infants (~25%) jaundice was noted to be present on the first day of life, corresponding to a mean TSB of ≥85 µmol/L

(≥5 mg/dL). The duration of NJ depended on its intensity. Thus in 89% of infants with 'moderate' NJ duration was <1 week, while in 75% of infants with 'marked' NJ duration was >1 week, and all infants with 'severe' NJ remained jaundiced for >1 week. Davidson *et al.* also refer to an apparently separate group of 120 infants for whom a total of 1,215 concomitant TSB values and clinical observations were available (4). These data make it clear that there is no fixed relationship between TSB and the absence respectively presence of NJ. Although NJ was not observed when TSB was ≤17 μmol/L (≤1 mg/dL), 'moderate jaundice' was noted in a handful of the 240 observations with TSB values between 17–34 μmol/L (1–2 mg/dL), increasing to about 50% of the observations with TSB values between 68–85 μmol/L (4–5 mg/dL) with a few additional observations categorized as 'marked jaundice'. With TSB values ≥205 μmol/L (≥12 mg/dL) about 80% of observations were in the 'marked jaundice' category, and the remainder were 'moderate jaundice' except for a single observation where NJ was not noted (4).

The US Collaborative Perinatal Project included data from 54,795 live births at 12 US centers from 1959-65 (38). TSB levels were obtained from 28,807 infants at 48 h of age, of these ~20% had TSB levels ≤52 μmol/L (≤3 mg/dL), while ~33% had TSB levels between 53–103 μmol/L (3.1–6 mg/dL). If we apply Kramer's data (1) and assume that the lower limit of our ability to visually detect jaundice in an infant is ~70 μmol/L (4 mg/dL), interpolating this assumption with the Perinatal Project data suggests that ~70% of these infants were jaundiced, while ~30% were not jaundiced at 48 h of age.

Osborn *et al.* followed 866 newborn infants with twice-daily clinical examination for jaundice, having first excluded 100 infants for prematurity, SGA, or illness requiring admission to their NICU (18). 80% of their cohort was Hispanic and 20% were Caucasian or African-American. Of these, 82% went on to develop clinical jaundice.

Maisels and Gifford measured TSB in 2,416 consecutive infants admitted to their well-baby nursery (20), and their data allow for an approximate comparison with the normal range for adults. In their total population 93% of the infants had a maximum TSB level that exceeded the normal adult range—among the breast-fed infants 94.2% exceeded this range and among the bottle-fed 91.5%. If we again assume that jaundice was detectable in infants with TSB ≥70 μmol/L (≥4.0 mg/dL) we can estimate that 72% of all infants were jaundiced (77% of the breast-fed *vs.* 66% of the bottle-fed) (20). These data appear very similar to those from the Collaborative Perinatal Project, as described above (38), in spite of the much higher rate of breastfeeding.

Corchia *et al.* followed 431 full-term Sardinian neonates with birth weight ≥2,500 G for 4 days with clinical assessment for NJ and then twice daily TSB tests for those found to be jaundiced (51). Of these, 71.9% were jaundiced and 28.1% were not jaundiced. However, because they were looking for factors contributing to increased risk for NJ, they excluded infants already known to have increased risk. These included infants who were G-6-PD-deficient, those who were not blood group compatible with their mothers, and infants who were preterm or low birthweight. Among infants with NJ, 47 (15.2%) had TSB values <137 μmol/L (<8.0 mg/dL). As the 121 non-jaundiced infants did not have TSB tests, we cannot know how many of them may have had HB. Also, it is reasonable to assume that the percentage of infants with NJ in the total birth population was higher than reported, given the exclusion of infants with known risk for NJ/HB (51).

Szabo *et al.* followed 140 healthy full-term neonates up to 6 days of life and compared data from clinical assessment of NJ according to Kramer's zones (assessed independently by a nurse and a pediatrician in daylight or 'warm white' fluorescent light), TSB measurement(s), and TcB measured by two different meters (Minolta Airshields JM-102 and BiliCheck respectively) (5). Some data can only be estimated from their figures, but apparently only 3/140 infants were judged clinically to be non-jaundiced, all 3 were hyperbilirubinemic as defined herein, although with TSB values ≤85 μmol/L (≤5.0 mg/dL). However, among the 16 infants judged to be jaundiced at Kramer's zone 1, one appears not to have been hyperbilirubinemic, and an additional five had TSB values ≤100 μmol/L (≤6.0 mg/dL) (5). No mention was made of feeding mode in this study.

Keren *et al.* examined 812 term and near-term infants with clinical assessment (by nurses) using the Kramer homunculus grading on, or close to, day 3 of life, as well as daily TcB measurements until discharge, supplemented with TSB if the TcB values exceeded preset values (52). Eighty-three percent of the infants were judged to be jaundiced, while 17% were not jaundiced. Bilirubin values for the non-jaundiced infants ranged from 0–215 μmol/L [0–12.5 mg/dL (mean =5)], the range was similar for both black and non-black infants. Also, it should be noted from this study that assessment of jaundice extent correlated poorly with TSB level in late preterm infants (35–38 weeks' GA).

Maisels *et al.* followed 1,044 predominantly breastfed infants of ≥35 weeks GA for a full month with TcB

measurements and clinical assessment. TcB values measured on the chest peaked at 3 days of life, at which time 94% of the measurements were ≥85 µmol/L (≥5 mg/dL) (39). Kramer zone scores were obtained on many infants during the month of follow-up but were not reported relative to day-of-life. However, it is noteworthy that for a Kramer zone score of 0, i.e., absence of jaundice, TcB values ranged from 0 to ~265 µmol/L (0–15.5 mg/dL), with a median of ~47 µmol/L (2.7 mg/dL). Bhutani *et al.* performed visual assessment of NJ at discharge from the nursery as well as TcB/TSB, and reported that 84% of the infants were clinically jaundiced (37). However, the Kramer scale data were not reported in detail, nor was the relationship with the TcB/TSB data.

The above 10 studies of NJ cover a full century and vary both as far as the methods employed for TSB (or TcB) analyses, the lighting conditions and techniques used to examine the infants for jaundice, and the feeding modes. Nevertheless, the following conclusions seem permissible:

(I) >90% of all newborn infants at some point(s) during the first days of life have HB as defined by TSB values that exceed the normal range for adults.

(II) The majority of newborn infants are judged to have NJ at some point during their first days of life, but the reported data for occurrence vary from 60% to nearly 100%, and are often not comparable because methods and criteria vary between studies.

(III) HB is often present even in infants who clinically do not appear jaundiced.

(IV) HB >205 µmol/L (>12 mg/dL) is rarely going to be missed by clinical assessment of NJ, but with few exceptions most studies show that our ability to judge the actual level of TSB by visual examination is limited.

Jaundice of the eyes may first have been described in 1,847 by Hervieux who autopsied 45 infants who had died while still jaundiced (53). Forty-four of these infants also had jaundiced brains, and among these 28 pairs of eyes were jaundiced. However, the relationship between TSB/TcB levels and jaundice of the conjunctiva in live infants was only studied recently (54-56). Importantly for clinical practice, the absence of conjunctival icterus helps to rule out significant HB (55,56). Also, parents may be advised to have their baby evaluated for NJ if they observe jaundice of the eyes (56). However, although the presence of conjunctival icterus is more common at intermediate-to-high TSB/TcB levels, in one of the studies it was also observed in ~20% of infants with TcB levels <171 µmol/L (<10 mg/dL) (55).

## Clinical course

The clinical course of NJ is characterized by the absence of jaundice at birth in the majority of infants, however with TSB values that exceed the normal range for adults (50,57). This is followed by an increase in TSB which eventually manifests with detectable jaundice, typically on the 2$^{nd}$–3$^{rd}$ day of life. However, infants with blood group isoimmunization may present with NJ on the very first day of life and then will require close follow-up and often therapeutic interventions (11,58). Historical data, before the advent of therapies that remove most of the higher TSB values, show that in the absence of interventions the peak of NJ as well as HB is reached later in those infants who go on to become very jaundiced (4,58). Thus, in Davidson's study from 1941, the infants on the 10$^{th}$ centile reached a peak TSB of ~27 µmol/L (1.6 mg/dL) on the second day of life, while infants on the 90$^{th}$ centile peaked at TSB ~220 µmol/L (12.8 mg/dL) on the fourth day of life (4). HB also lasts longer in infants at the higher centiles, resulting in a greater 'area under the curve' as far as exposure to bilirubin. This may be predicted by early measurement of TSB and/or TcB and charting the values on a nomogram relative to an infant's age in hours (26,59). Similar findings were made by Fouzas *et al.* who constructed a nomogram based on TcB measurements taken twice daily during the first 5 days of life in late preterm infants (60). TcB values peaked on the 3$^{rd}$ day of life in infants on the 5$^{th}$ and 25$^{th}$ centile, between the 3$^{rd}$ and 4$^{th}$ day of life in infants on the 50$^{th}$ centile, and on the 4$^{th}$ day of life in infants on the 75$^{th}$ and 95$^{th}$ centile. In a larger study that also included many term infants ≥37 weeks GA, TcB values for both the 50$^{th}$, 75$^{th}$, and 95$^{th}$ centiles peaked at 4.5 days of life (61). Postl *et al.* compared the course of neonatal HB in Inuit *vs.* Caucasian infants, and found that the former had higher peak TSB values than the latter, and reached these on day 3 of life, *vs.* day 2 for the Caucasian infants (62).

Recently, Kaplan and Maisels used pooled readings from 19 published TcB nomogram reports from predominantly breastfed newborns ≥35 weeks gestation to construct a 'universal' TcB nomogram which included the 25$^{th}$, 50$^{th}$, 75$^{th}$, and 95$^{th}$ percentiles from 12 to 120 h (63). Studies included >119,000 TcB measurements from 44,392 infants and had been performed in the Americas, Europe, Africa, and Asia. This large data set confirms the relationships between percentiles and the age at which bilirubin values

reach their peak, as discussed above. Thus, factors that modulate the clinical course of NJ may also impact on the epidemiology of NJ as well the risk for bilirubin-related sequelae.

## Factors that influence the epidemiology of NJ

### *Ethnicity*

Infants of Southeast and Far East Asian descent have, on average, higher TSB concentrations and more NJ than infants of Caucasian or African descent (27,36,44,64-67), as do some American First Nation peoples (68) and Inuits (62,69). A comparison of the different ethnic groups in Singapore in the 1960s found clinical NJ in 90% of Chinese infants in the 1st week of life compared to 70% in Malays, and 30% in European infants (70). In the same study 99% of Chinese infants reached a peak TSB of ≥70 µmol/L (≥4 mg/dL), while 69% had levels of >170 µmol/L (>10 mg/dL). Peak TSB values were reached between the 2nd–3rd days of life in European infants *vs.* between the 4th–5th days of life in Asian infants. Of note, NJ/HB due to Rhesus iso-immunization is very rare among Chinese neonates since more than 99.9% of Chinese are Rhesus positive (71). In a study in Nepal (n=18,985) Infants of Madeshi ethnicity (originating from the plains) had a decreased risk of jaundice compared to infants of Pahadi (originating from the hills) ethnicity [RR =0.21 (95% CI: 0.18–0.25)]. However, it should be noted that infants in Madeshi households were significantly less likely to be exclusively breastfed, to be started on feeding early, or be given colostrum compared with Pahadi infants, all of which may confound the interpretation of the role of ethnicity (72).

In infants of mixed Asian-Caucasian parentage, only having a Caucasian mother and an Asian father was associated with increased probability of having a discharge diagnosis of NJ (67). Among 2,272 Nigerian infants examined daily for NJ during the first week of life, 35% of males and 30% of females were found to be jaundiced (73). The onset of NJ was on the 1st day of life in 12.8%, and between the 2nd–4th days in 72.4% of the cases. In cases with NJ, TSB was >170 µmol/L (>10 mg/dL) in 32.4%, less than half of the incidence in the Chinese infants, as mentioned above. Etiologic factors were sought in the 125 infants who had TSB >257 µmol/L (>15 mg/dL), the leading contributory cause was G-6-PD-deficiency in 49/125 cases, 37/125 had AB0-incompatibility (in combination with G-6-PD-deficiency in 11), while only 2/125 had Rhesus-incompatibility (73). Newman *et al.* compared the incidence of 'non-physiologic' HB in infants discharged from a hospital in San Francisco, CA, USA and found that the incidence was 31% in infants of Asian parentage, 16% in Caucasians, and 9% in African-Americans (66). The timing of presentation of HB differed between ethnic groups. Thus, while almost 80% of African-American infants with 'non-physiologic' HB had these values noted during the first 2 days of life, this occurred in 64% of Caucasians and 55% of Asians respectively (66).

### *Geography*

In infants born on the island Lesbos in Greece NJ was found to be more frequent and more pronounced in both normal and in G-6-PD-deficient infants than in similar infants on the island of Rhodes as well as in a general Greek cohort of infants (74,75). This phenomenon may not present in infants of Greek parentage born elsewhere in the world (76). It has been suggested, but apparently not as yet documented or agreed, that an environmental factor may contribute to this phenomenon (77-81). It is interesting that a high incidence of NJ was also found on another Mediterranean island, Sardinia (51). In the study from Lesbos 'severe NJ' was defined at TSB >274 µmol/L (>16 mg/dL), and the incidence can be calculated from their table II to be 10.9%, while the incidence in Sardinia was 8.8%, excluding cases of G-6-PD-deficiency and blood group incompatibility (51,74).

A comparison of infants born at 3,100 *vs.* 1,600 m altitude in Colorado showed that the incidence of HB >205 µmol/L (>12 mg/dL) was 32.7% at the higher *vs.* 13% at the lower altitude, and about 4 times that of data from sea level (16). A comparison of factors that influence serum bilirubin levels did not point to any factor(s) other than altitude that could explain the higher incidence of HB at 3,100 m. Although hematocrit values were significantly higher at 3,100 *vs.* 1,600 m, the differences were rather small, and in both cohorts hematocrit values were actually higher in infants without HB than in infants with HB. Thus, a higher Hgb load leading to greater bilirubin production does not seem a likely explanation for the difference in HB incidence. The authors speculated that uptake or conjugation, but not excretion, might be impaired by high altitude exposure (16,82).

Ding *et al.* followed 875 newborns from three different geographical areas of China (North, Northeast, and South) with TSB measurements during the first 7 days of life (27). In all areas peak TSB values were reached on the 5th day of life. However, with the exception of day 1 of life, infants from

the South had significantly higher TSB values throughout the period of observation, while those from the Northeast had the lowest values and those from the North occupied an intermediate position (27). The study did not bring to light any concrete explanations for these differences, but the authors speculated that differences in local customs and heredity might contribute.

### *Season*

Milby *et al.* first reported seasonal variations in the incidence of neonatal HB (14). A retrospective review of nursery records in a small California community hospital revealed a significantly higher number of cases of HB exceeding 170 µmol/L (10 mg/dL) in the 4$^{th}$ quarter (October–December) of each of 4 succeeding years. The authors speculated on a number of hypothetical explanations for their findings without identifying a specific cause. A prospective study was undertaken and alluded to in later correspondence, but no data have been published (83).

Lee *et al.* studied neonatal HB in Hong Kong, defined as TSB >257 µmol/L (>15 mg/dL), over a period of 4 years, and found that HB was significantly more common in summer (April–September) than in winter (October–March) (71). Friedman *et al.* retrospectively analyzed the occurrence of HB [≥205 µmol/L (≥12 mg/dL) and ≥291 µmol/L (≥17 mg/dL)] among 12,461 neonates over a 5-year period in a London birthing hospital (84). Although their data were collected by month and shown in their figure 1, they apparently did not perform a statistical assessment of seasonal variation. Nevertheless, an inspection of that figure shows that with the exception of the 3$^{rd}$ year, the peak incidence of HB occurred mid-year, while in the 3$^{rd}$ year the peak incidence looks to be shifted a couple of months toward early fall (84).

In a study of 875 newborns from three geographical regions of China, Ding *et al.* found that mean TSB values on the first 4 days of life were significantly higher during the months of April–June than during the other quartiles of the year (27). González de Dios *et al.* in Alicante, Spain studied NICU admissions and found significantly higher rates of 'severe HB' in the summer, speculating that temperatures might have an influence (85). Cerna *et al.* compared two groups of healthy neonates born in June and December respectively for HB >205 µmol/L (>12 mg/dL) and use of phototherapy (86). Both HB as defined and phototherapy use were significantly more prevalent in June than in December (27.5% *vs.* 22.9%, P<0.05, and 14.3% *vs.* 10.0%, P<0.05, respectively).

Similarly, in Nepal birth during the "hot season" (March–October) was significantly associated with NJ (72). This was further validated by the recorded minimum ambient air temperature on the infant's birthdate, which indicated a significant 3% increase in risk of NJ for each 1 ℃ increase in temperature. Identification of NJ was by visual inspection by study case workers (72).

Thus, several studies seem to suggest that the incidence of NJ may vary with season, and with the exception of one study (14), all appear to find a higher incidence in summer or warm season. However, all studies except for the one in Nepal (72) were small and/or retrospective and their criteria for case inclusion differed. In conclusion, the data that show a seasonal variation in the incidence of NJ are suggestive but limited, and further prospective studies with well-defined criteria are needed to answer this question.

### *Family*

Lower birth order and an older sibling with NJ have both been shown to be associated with increased risk of NJ (24,51,72,87). Nielsen *et al.* found that when a woman had born a severely jaundiced infant, the risk of a recurrence in her next pregnancy was 2–3 times greater (88). Almost identical observations were made by Khoury *et al.*, i.e., the risk of NJ in newborns who had older sibling(s) with NJ was 3.1 times greater than for those without such family history (89). Further, the risk of severe HB (defined as peak TSB >257 µmol/L) in newborns who had older sibling(s) with severe HB was 12.5 times higher than that of control newborns (89).

### *Genetics*

Both the ethnic and familial factors discussed above are likely to have genetic causes. A number of well-described syndromes are associated with NJ, such as hemolytic anemias, variants in bilirubin metabolism, and Down syndrome. As the genetics of NJ is reviewed in another paper in the present issue of Pediatric Medicine, this topic will not be discussed further here.

### *Events during pregnancy*

#### Maternal smoking

Hardy and Mellits first suggested that maternal smoking

reduced NJ, however the sample size was small and they did not control for other factors that might influence TSB levels (90). Similar claims were made shortly thereafter by Nymand, but no details of the study were reported (91). Also, in a large retrospective study based on interviews and record reviews Linn *et al.* found a significant negative correlation between maternal smoking and HB ≥171 µmol/L (≥10 mg/dL) (19). The findings were sustained in a logistic regression controlling for other potential contributing factors (OR: 0.77, 95% CI: 0.68–0.87). Interestingly, a very similar odds ratio, using the same cutoff value for TSB to define NJ, was found by Diwan *et al.* (OR: 0.81, 95% CI: 0.66–0.99), although they started by identifying infants with NJ, then selecting controls (23). In a recent large Swedish registry-based study of 1,019,220 singleton live births between 1987–2002, Lee *et al.* showed that maternal smoking was significantly associated with a reduced incidence of both hemolytic and non-hemolytic NJ, with odds ratios between 0.73–0.88, perhaps providing the most convincing evidence for this association (92).

In a population of 10,122 singleton Israeli newborns Gale *et al.* identified 1,154 infants with TSB >221 µmol/L (>12.9 mg/dL) (24). An equal number of controls were selected at random from the remaining infants who all had lower TSB values. There was no difference in the number of mothers who smoked during pregnancy between the two groups. However, <4% of mothers in both groups reported smoking in pregnancy—a significantly lower proportion than in other populations. Thus, in a smaller study from Denmark performed at the same time as the study from Israel, 43% of mothers reported smoking during pregnancy (93). The median increase in TSB during the first 24 h of postnatal life was significantly higher in the group of neonates born to smokers compared to non-smokers (P<0.02), while in contrast the median increase in TSB from the 1st to the 3rd postnatal day was significantly lower among the neonates born to smokers compared to non-smoking mothers (P<0.04). Thus, on the 3rd postnatal day the overall frequency of clinical jaundice and the frequency of neonates with TSB >175 µmol/L was almost identical in the two groups (93).

In conclusion, several studies suggest that maternal smoking may reduce NJ/neonatal HB, although not all studies concur. Several mechanisms for this effect have been suggested, but no direct experimental evidence for these appears to have been published. Future studies need to control better for breast-feeding as a possible confounder, as smoking mothers may breastfeed less than nonsmokers (94).

**Maternal age and illness**

Studies are divided as far as the effect of maternal age on the incidence of NJ. Thus, while some found the incidence to be increased in older mothers (24,92,95,96), others found the highest risk in infants of younger mothers (72,97,98), particularly in those <20 years of age (72,98).

A higher incidence of NJ/neonatal HB is associated with maternal diabetes, pregnancy-induced hypertension, maternal obesity, and 1st trimester bleeding (19-22,24,92).

**Maternal pharmacotherapy**

Drugs may induce liver enzymes (99,100). When given to pregnant women phenobarbital has been shown induce hepatic processing of bilirubin in the fetus (101,102). In Malawi infants born to HIV-positive mothers who had received a 6-week course of nevirapine to reduce mother-to-infant virus transfer, were shown to have significantly reduced incidence of NJ compared to infants of mothers who were HIV negative and had not received nevirapine (103). Nevirapine is known to interact with cytochrome P450 enzymes both as a substrate and as an inducer, and the latter probably explains the effects noted (104). Oxytocin administered at delivery has been shown by some to be associated with NJ, however the effects were small and not replicated by others (19,21,84).

### *Blood group incompatibility*

Because bilirubin is the end product of heme catabolism, increased breakdown of erythrocytes, as occurs in all kinds of hemolytic anemias, increases bilirubin production causing NJ (105). Hereditary hemolytic anemias are dealt with elsewhere in this issue of the journal. However, hemolysis through immune mechanisms elicited by maternal-fetal blood group incompatibilities is a more common contributor to NJ, and among these ABO incompatibility has become the most frequent in clinical practice (24,37,106,107). The incidence of Rh isoimmunization has declined significantly since the advent of Rhesus prophylaxis in pregnancy, however it remains an important cause of neonatal morbidity and mortality (36,108,109). Among less common blood group incompatibilities Kell, s, C, Jka, S, Lub, and N isoimmunization may cause significant hemolytic disease of the newborn (110,111).

### *Labor and delivery*

Several events related to labor and delivery have been

found to be associated with increased NJ/HB, including placenta previa, placental abruption, PROM, prolonged labor, breech presentation, forceps, vacuum, caesarean delivery, epidural anesthesia, and cephalohematoma (19,24,51,72,84,107,109). However, some nuances should be noted. Thus, Bracci *et al*. found higher TSB after spontaneous delivery *vs.* emergency caesarean, and after planned *vs*. emergency caesarean delivery (107). Also, Friedman *et al.* found that general anesthesia reduced the risk for NJ/HB (84).

### *Gestational age/prematurity*

Lower gestational age increases the risk for NJ (19,24,37, 60,84,107,112-116). Thus, for each week of gestation below 40 weeks, the risk for significant HB increases significantly (96,117-119). Prediction is further improved by including predischarge TSB/TcB (118). Although low gestational age predicts an increased need for PT, this is likely, at least in part, also an effect of chart construction (24,120,121).

### *Birth weight*

Low birth weight is also associated with increased risk for NJ (18,19,21,24,72,84,107,109,113).

### *Gender*

The risk of NJ is increased in male newborns compared to females, as has been shown in multiple studies (19,24,51,60,72,76,84,107,111). However, the mechanism for this phenomenon appears not to have been discussed.

### *Nutrition, caloric intake, fluids, weight loss*

A proportion of breast-fed infants exhibit exaggerated and prolonged HB during the first days and weeks of life (12,15,18-20,28,39,107,109), and breastfed infants had significantly greater need for PT than controls (18,37). It may take from 1–4 months of slowly declining TSB levels before values normalize (12). In one study, among infants with feeding difficulties exclusive breastfeeding was a risk factor for NJ, whereas exclusive breastfeeding was protective among infants with no report of feeding difficulties (72).

The degree of NJ/HB in the neonatal period is associated with percent postnatal weight loss (24,51,122), and maximum dehydration as well as time to maximum dehydration is greater in jaundiced infants *vs.* controls (18).

### *Meconium retention vs. passage*

Corchia *et al.* showed that delayed first passage of meconium is associated with greater risk of NJ (51).

### *Hemorrhage/bruising/fractures*

Any extravasation of blood, as in fractures, hematomas, and closed hemorrhages increases the likelihood of NJ/HB (24,37,112).

### *Polyglobulia/polycythemia*

High hematocrit during the first days of life is associated with increased risk of NJ/HB (12,107,109,123). However, late cord clamping had no effect on TSB course or the need for PT, though the hematocrit increased by only 2.7 percentage points (124).

### *Infection/sepsis*

NJ may on rare occasions be the presenting sign of infection such as sepsis and UTI (19,33,112,125-128).

### *'Pronounced', 'severe', 'extreme', and 'hazardous' HB*

With some variations depending on the complexities of the birth population and/or the conformation of therapeutic guidelines, about 5% of healthy term and near-term infants receive PT for NJ/HB. Certain risk factors have been shown to be strongly predictive of such 'pronounced' NJ, including lower GA, bruising, blood type incompatibility with or without positive DAT, Asian ethnicity, exclusive breastfeeding, and extent of jaundice in Kramer zones (37). The same is true for TSB ≥100 µmol/L (≥6 mg/dL) during the first 24 h of life and TcB values above the 75$^{th}$ centile on the Bhutani nomogram between 24–72 h of life (26,129). Re-hospitalization for NJ is associated with a need for phototherapy in the majority of infants (130). Risk factors associated with re-hospitalization include ethnicity (Caucasian or Asian), primiparity, preterm birth, breast-feeding, feeding difficulties and suspicion of jaundice during the birth hospitalization, and early discharge (<48 h) compared to later discharge, particularly for infants of 37 and 38 weeks GA compared to those of 39–41 weeks GA (40,130,131).

Worldwide the incidence of 'severe' NJ, defined as

jaundice associated with acute bilirubin encephalopathy (ABE)/kernicterus and/or exchange transfusions (ET) and/or jaundice-related death, has been estimated by Slusher *et al.* to be 99/100,000 live births (95% CI: 28–356) (132). No TSB values were available for this study, but given the severity of the clinical symptoms included in the study, it seems very likely that a large proportion of these infants will have had TSB values in the 'extreme' and even 'hazardous' range (12). The study demonstrated very significant disparities between parts of the world, from a low estimate of 37/100,000 (95% CI: 17–80) in Europe to a high of 6,678/100,000 (95% CI: 6,033–7,385) in Africa (132). During the past 60+ years several studies have estimated the incidence of 'severe' NJ, starting with the reanalysis of data from the US Collaborative Perinatal Project that showed an incidence of 707/100,000 live births (133). The methods for detecting patients have varied between studies, from clinical detection of NJ in single centers leading to TSB testing, to TSB screening of complete cohorts in multiple hospitals (32,112,116,119,131,134-143). Not surprisingly, the incidence range has been very wide, from 10.4/100,000 (140) to 6,600/100,000 (141), though the latter was based on the rate of ET.

Bhutani *et al.* estimated that the incidence of 'extreme' NJ [defined as TSB >428 µmol/L (>25 mg/dL)] worldwide was 359/100,000 live births, and that about 24% of the affected infants died, while 13% were left with moderate-to-severe long-term neurological impairments (36). In other studies the incidence of 'extreme' NJ varied from 9.4/100,000 to 233/100,000 (32,43,49,116,119,133,134,136,139,140,143,144). The incidence of 'hazardous' HB [TSB >510 µmol/L (>30 mg/dL)] ranged from 2/100,000 to 15/100,000 (32,49,131,134,139,140,145-147).

Applying even the moderate estimate of 'severe' NJ from Slusher *et al.* (132) to the 130 million births per year in the world translates into ~130,000 newborn infants each year who are exposed to significant risk of bilirubin-induced brain damage or death. Therefore, as the risk factors for 'severe' NJ may vary between countries and regions, depending both on biological differences and different ways of organizing health care, each region, country, and/or institution should analyze their risk profile and educate their caregivers as well as their birthing population to these to reduce the risk of kernicterus spectrum syndrome and death (147). Some risk factors are global, such as blood group incompatibility, prematurity, breast-feeding jaundice, extravasation of blood, male gender, family history (previous sibling with NJ), and hospital readmission (47). Others may show significant variation between regions, such as ethnicity (Southeast Asian) and G-6-PD-deficiency (47). However, in a significant proportion of cases no specific etiology is found, highlighting the need for vigilance and an 'open door' policy for expedient management of all infants with NJ (148,149).

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