First of two parts

Jaundice in a newborn

Answers to questions about a common clinical problem

BY M. JEFFREY MAISELS, MB, BCH

Yes, jaundice in newborns is prevalent and usually benign, but these babies still need ongoing clinical assessment. Part 1 reviews ways to identify and categorize hyperbilirubinemia and sets out the testing that a jaundiced infant requires.

Approximately two of three newborns appear jaundiced at some time during their first week of life. This means that you and your colleagues manage jaundiced infants almost every day. The great majority of these infants remain healthy but, in rare cases, serum bilirubin rises to a level that is toxic to the central nervous system.

Hyperbilirubinemia occurs when the liver cannot clear enough bilirubin from the plasma. In the newborn, the problem is often a combination of excessive bilirubin formation (some degree of hemolysis) and impaired conjugation leading to unconjugated (indirect-reacting) hyperbilirubinemia. When excretion of bilirubin glucuronide (conjugated bilirubin) is impaired, conjugated (direct-reacting) hyperbilirubinemia or cholestatic jaundice develops.

Why a jaundiced newborn warrants ongoing clinical attention, how to identify those infants at risk of severe hyperbilirubinemia, and how to prevent bilirubin toxicity are the topics of discussion in this two-part review. That discussion deals almost exclusively with indirect hyperbilirubinemia.

Why be concerned about jaundice?

Be concerned because kernicterus—the chronic sequelae of bilirubin encephalopathy—continues to occur. For this reason and others listed in Table 1, jaundice

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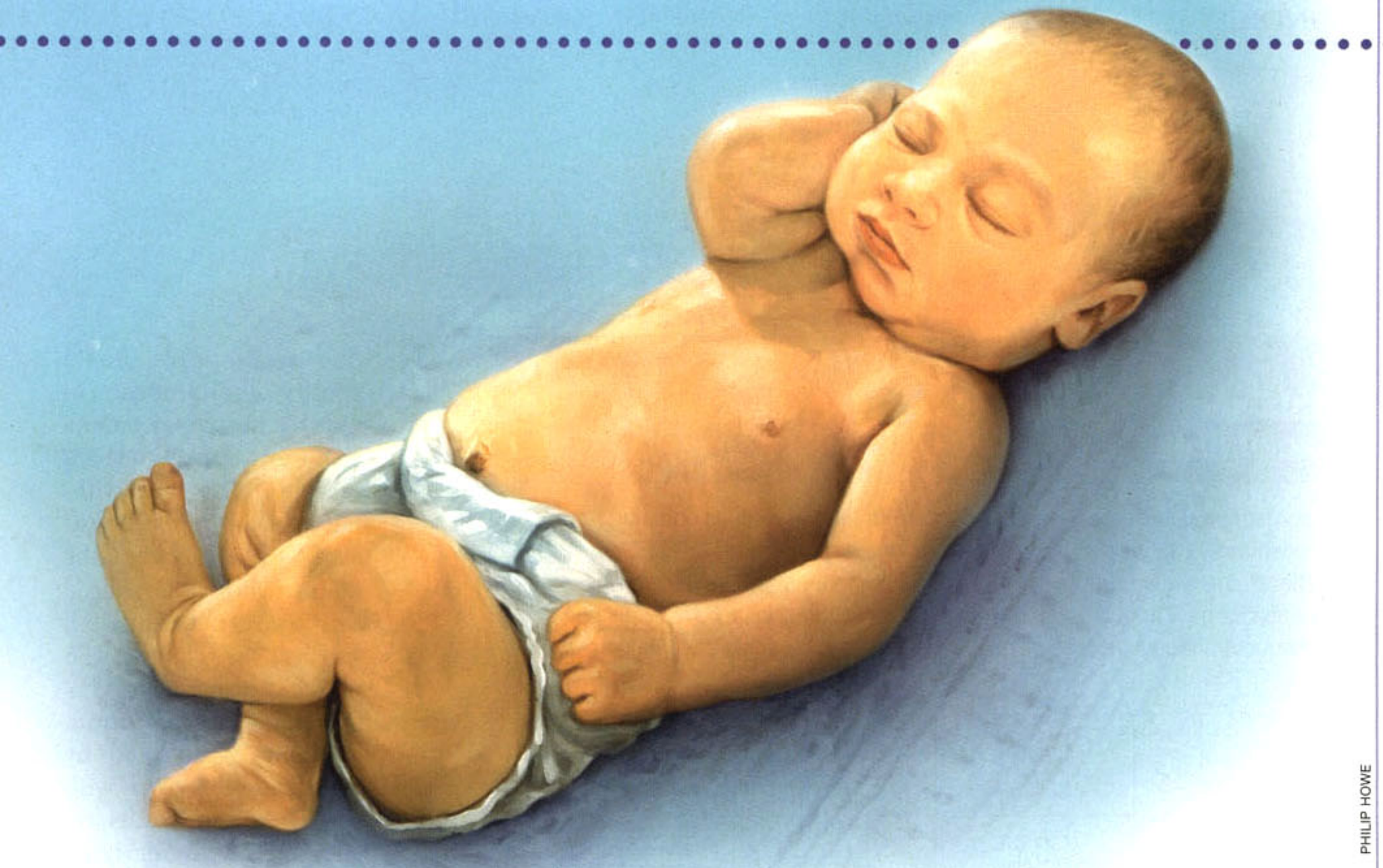


PHILIP HOWE

requires the attention of pediatricians,[1] and our approach to the jaundiced newborn needs to change—in terms of both increased vigilance and how we interpret bilirubin measurements.

Kernicterus has not disappeared. As described in the article on page 57 of this issue,[2] kernicterus still occurs, and it produces the same devastating neurodevelopmental consequences—a choreoathetoid type of cerebral palsy (CP), hearing loss, gaze palsy, and dental dysplasia. Bhutani and colleagues identified 125 infants in the kernicterus registry who were born between 1984 and 2002 and discharged as "healthy newborns" but who nonetheless developed kernicterus.[3]

At least 5,000 new cases of cerebral palsy occur annually in the US,[4] and at least 80% of these cases result from prenatal events over which neither you nor the obstetrician have any control.[5] Kernicterus, although a rare event, is one cause of CP, but *it is almost always preventable through a relatively straightforward process of identification, monitoring, follow-up, and treatment of the jaundiced newborn.* You are obliged to monitor and treat many jaundiced infants—most of whom will be perfectly normal—to prevent substantial harm to a few.

Early discharge increases the risk of severe hyperbilirubinemia. It is not entirely clear why kernicterus still occurs—its incidence may have even increased in the last decade or two—but an important factor appears to be the early discharge of term and near-term newborns (35 to 38 weeks' gestation) coupled with lack of follow-up within two days of discharge.

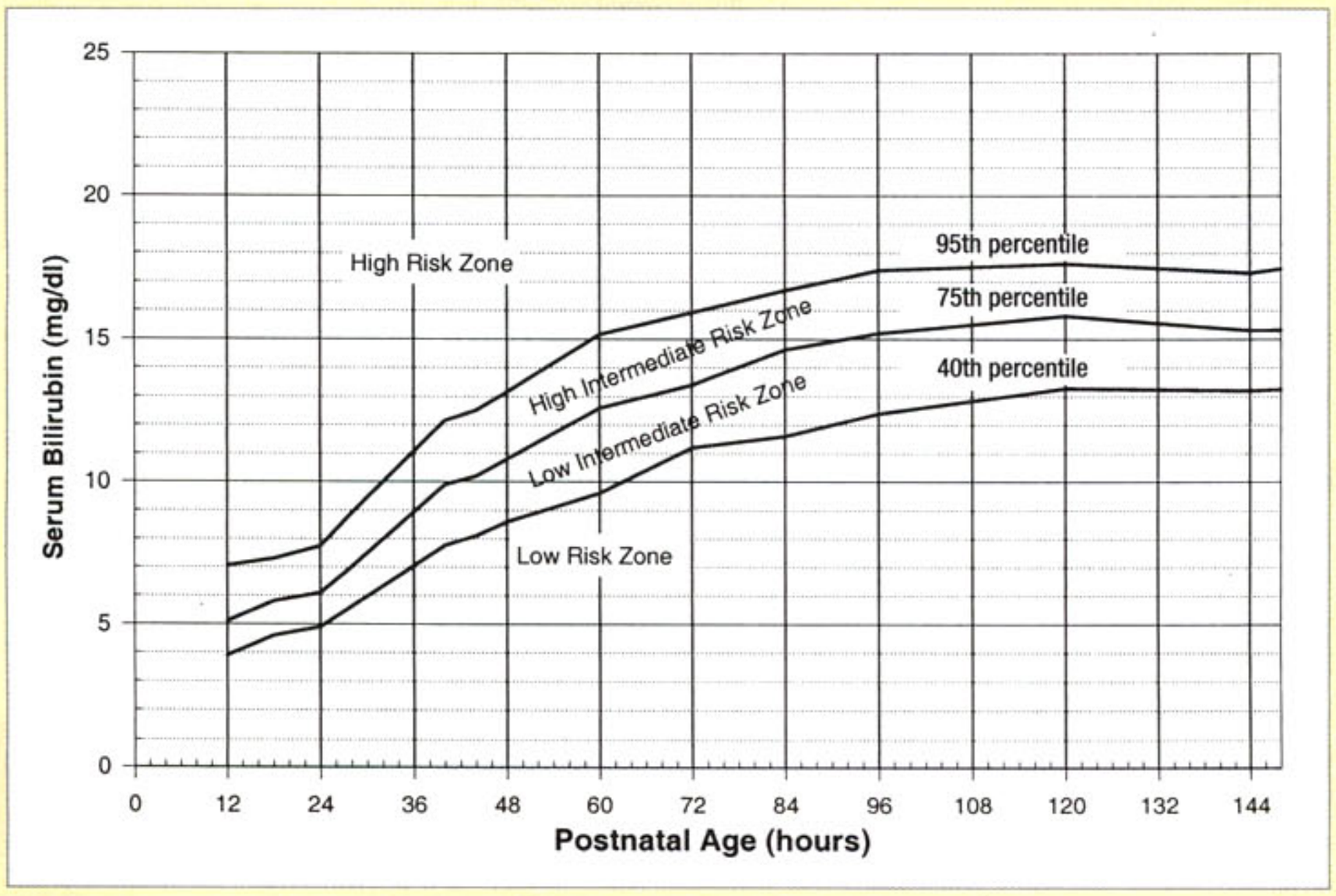
Total serum bilirubin (TSB) generally peaks at 3 to 5 days. In the era when newborns remained in the hospital for three or four days, jaundiced babies could be identified before discharge and appropriately evaluated and treated. Today, because almost all infants delivered vaginally leave the hospital before they are 48 hours old, the bilirubin level peaks when they are home. Figure 1 makes it clear that, *at discharge, the TSB in these infants is likely to be going in one direction: up.*

Some studies have found that early discharge itself is associated with an increased risk of significant hyperbilirubinemia.[6-8] In light of the connection between severe jaundice and early discharge, the American Academy of Pediatrics (AAP) provides stringent guidelines for follow-up of all infants discharged before 72 hours of age.[9]

FIGURE 1

Establishing "risk zones" of hyperbilirubinemia in newborns

This nomogram is based on hour-specific serum bilirubin values obtained from 2,840 well newborns ≥36 weeks' gestational age with a birth weight ≥2,000 g or ≥35 weeks' gestational age with a birth weight ≥2,500 g. The serum bilirubin level was obtained before discharge. The risk zone in which the value fell predicted the likelihood of a subsequent bilirubin level being abnormal—that is, exceeding the 95th percentile.



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Shorter stays necessitate a change of thinking on our part: TSB levels must be interpreted in terms of the infant's age in hours, not days. Although clinicians often discuss jaundice occurring on Day 2 or Day 3, Figure 1 illustrates how misleading this thought process can be.[10] A TSB level of 8 mg/dL at 24.1 hours is above the 95th percentile and calls for evaluation and close follow-up, whereas the same level at 47.9 hours is in the low-risk zone and probably warrants no further concern. Yet, both values occur on Day 2.

How should a jaundiced newborn be identified and categorized?

Table 2 lists the essential components of a protocol for identifying and monitoring jaundiced babies in the nursery. Protocols should specify conditions in which a nurse may order a TSB or transcutaneous bilirubin (TcB) level without consulting a physician.[9] An example is the infant who is jaundiced before age 24 hours. All such infants require a TSB or TcB measurement.[11]

Visual identification. Jaundice is detected by blanching the skin with digital pressure, thus revealing the underlying color of the skin and subcutaneous tissue. Perform this assessment in a well-lit room or, ideally, in daylight by a window.

Jaundice progresses in a cephalocaudal fashion, starting in the face and moving to the trunk and extremities.[12] Infants whose jaundice is limited to the face have a lower bilirubin level than those with jaundice on the chest or abdomen, but the range of TSB levels within these zones of observation is wide.[12,13] The ability to estimate a bilirubin level from the degree of jaundice also varies widely and can lead to errors,[13,14] especially in a darkly pigmented infant. For example, the difference between a TSB level of 5 mg/dL and 8 mg/dL cannot be perceived by the eye; yet, at 24 hours, that 3 mg/dL is the difference between a TSB level below the 40th percentile and one at the 95th percentile (Figure 1).

One response to the difficulty of determining, visually, the degree of hyperbilirubinemia is for you to measure the TSB or TcB on every baby before discharge and repeat the measurement at different intervals, depending on the level.[2] This should certainly be done if you have doubts about the severity of the jaundice or if follow-up cannot be assured. The AAP recommends that

you use a low threshold to measure TSB in the nursery and at follow-up visits, and that all infants discharged at less than 72 hours of age be seen within two days after discharge—earlier if multiple risk factors are present (these are discussed in Part 2 of this article).[9]

Noninvasive bilirubin measurement. Two hand-held electronic devices are available for measuring TcB: the BiliChek (Respironics) and the Konica Minolta/Air-Shields JM-103 (Air-Shields). These instruments provide an estimate of the TSB level, and a close correlation has been found between TcB and TSB measurements in different racial populations.[15,16]

TcB measurement is not a substitute for TSB measurement, but TcB can be helpful. When used as a screening tool, TcB measurement can help you to answer the questions "Should I worry about this infant?" and "Should I obtain a TSB on this infant?"[17] The measurements are also useful for following the trend of the TcB.[17]

Because the goal is to avoid missing a significantly elevated TSB, you might set a value for the TcB measurement (based on the infant's age in hours and other risk factors) above which a TSB level will always be obtained. For example, you could obtain a TSB whenever the TcB is above the 75th percentile.

In a study at my institution in which the JM-103 device was used, the TSB was 3 mg/dL or more greater than the TcB measurement in only five of 849 infants.[15] So, another approach would be to add 3 mg/dL to the TcB measurement; if this level (TcB +3) would change your management, then measure the TSB. This approach is likely to detect babies with significant hyperbilirubinemia while sparing many infants and families the trauma, cost, and inconvenience of having a laboratory measurement of serum bilirubin.

Measuring TcB significantly reduces the need to measure TSB in the nursery,[18] office, and clinic. At my hospital, we use the JM-103 to screen infants daily. In 2004, only 9% of some 6,000 infants in our well-baby nursery required a TSB measurement.

When is the TSB level considered abnormal?

Based on studies in the US that found that 95% of infants had a TSB concentration of 12.9 mg/dL or lower,[19,20] 12.9 mg/dL (the 95th percentile) became the accepted upper limit of "physiologic jaundice." More recent studies show that, by 96 hours, TSB levels of about 17 mg/dL represent the 95th percentile,[10,21] suggesting that the incidence of jaundice in newborns is increasing. One likely reason for the change in the TSB level in the US population is the great increase in the percentage of mothers who are breastfeeding at discharge—up from 30% in the 1960s to 65% today (more on the role of breastfeeding later).[22]

The TSB level varies considerably, depending on race, prevalence of breastfeeding, and other genetic and epidemiologic factors.[23,24] Although it can be difficult to agree on what, precisely, a "normal bilirubin level" is, one finding is clear: *Because the TSB is constantly changing in the hours to days after birth, you must interpret all TSB levels in terms of the infant's age in hours.*

The nomogram on page 36 makes identification of an abnormal TSB relatively straightforward: It is one that is either above the 95th percentile or is increasing and crossing percentiles.[10] The 95th percentile in this nomogram also represents a rate of rise of TSB of 0.2 mg/dL/hr. Infants whose TSB is increasing by more than this rate should be evaluated and followed closely.

Plotting the infant's TSB level on the nomogram tells you when to be concerned about the TSB level (investigate the cause, follow up with additional TSB measurements) and quantifies the risk of the infant developing, or not developing, hyperbilirubinemia. (In fact, the nomogram is most accurate in predicting which infants

are *not* at risk of significant hyperbilirubinemia.) Numerous studies have confirmed its value as a tool for predicting hyperbilirubinemia,[10,23,25-29] and the AAP recommends it for this purpose.[9]

Should pediatricians seek a cause for jaundice?

In some infants, the cause of hyperbilirubinemia is apparent from the history and physical examination; most jaundiced infants don't need a workup for you to determine why they are jaundiced. Moreover, most of the laboratory tests usually performed to find a cause for jaundice (CBC, hematocrit, reticulocyte count, blood smear) are neither sensitive nor specific and, more often than not, do not lead to a specific diagnosis.[20,30] Two exceptions are the blood type and the direct Coombs test (also called the direct antiglobulin test, or DAT), which identifies antibodies attached to the red blood cell.

Jaundice in a severely bruised infant needs no further explanation; nor do you need to investigate *why* a 4- to 5-day-old breastfed infant whose TSB level is 15 to 16 mg/dL is jaundiced. In both cases, though, follow-up is necessary to ensure that the bilirubin level does not become excessive.

In an otherwise normal infant, look for a cause of the jaundice if:

- the infant needs phototherapy

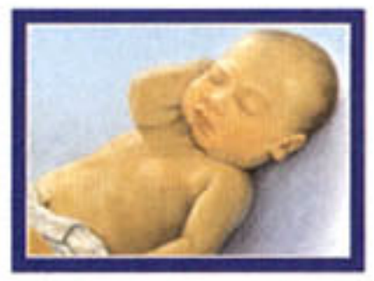
or

- the TSB level is rising rapidly and crossing percentiles and this cannot be readily explained by the history and physical examination.

If the TSB is above the 75th percentile, perform a blood type and Coombs test, and consider ordering a test for glucose-6-phosphate dehydrogenase (G6PD) deficiency—particularly if the infant is black. Because Coombs-positive isoimmune hemolytic disease[31,32] and G6PD deficiency are risk factors for bilirubin encephalopathy, you need to know whether either is present so that phototherapy or exchange transfusion can be initiated at a lower bilirubin level than usual. Table 3 lists the indications for laboratory evaluation of a jaundiced infant.

By measuring end-tidal carbon monoxide in our nursery, we have found an increased rate of bilirubin production in four of five infants whose TSB level is above the 75th percentile. This suggests that some degree of hemolysis is a contributing factor in most infants who are jaundiced in the first few days after birth.[33]

Most pediatricians do not readily consider a diagnosis of G6PD deficiency, but you should—particularly in a jaundiced black infant. In the US, 11% to 13% of African-American newborns are G6PD deficient and, in the kernicterus registry, G6PD deficiency was consid-



ered the cause of the hyperbilirubinemia in 26 of 125 infants (21%).[3] Because black infants as a group have a much lower TSB level than white infants do,[30] significant jaundice in a black infant should always raise the possibility of G6PD deficiency.

When is the direct bilirubin level cause for concern?

If the TSB is less than or equal to 5 mg/dL, consider a direct (or conjugated) bilirubin level greater than 1 mg/dL to be elevated. For a TSB level greater than 5 mg/dL, consider a direct bilirubin of more than 20% of the TSB to be abnormal. If the laboratory measures conjugated bilirubin using the Vitros system (Ortho-Clinical Diagnostics), consider any value greater than 1 mg/dL to be abnormal. Other clinical laboratory instruments measure direct-reacting bilirubin.*

Elevated direct-reacting bilirubin could be an early sign of urinary tract infection; you should perform urinalysis and urine culture. Also consider undertaking a sepsis evaluation. Late onset of jaundice (after the fourth or fifth day) has also been associated with urinary tract infection.[34]

Any sick baby who is jaundiced should have total and direct bilirubin measured to identify cholestasis. And, even though it is common to see a 3-week-old, jaundiced breastfed infant (some healthy, breastfed infants have indirect hyperbilirubinemia for as long as three months[35]), *any infant still jaundiced at 3 weeks of age must have total and direct bilirubin measured at least once* to identify cholestasis and to diagnose biliary atresia early. Results of the newborn thyroid and galactosemia screens should also be checked in these infants.[9]

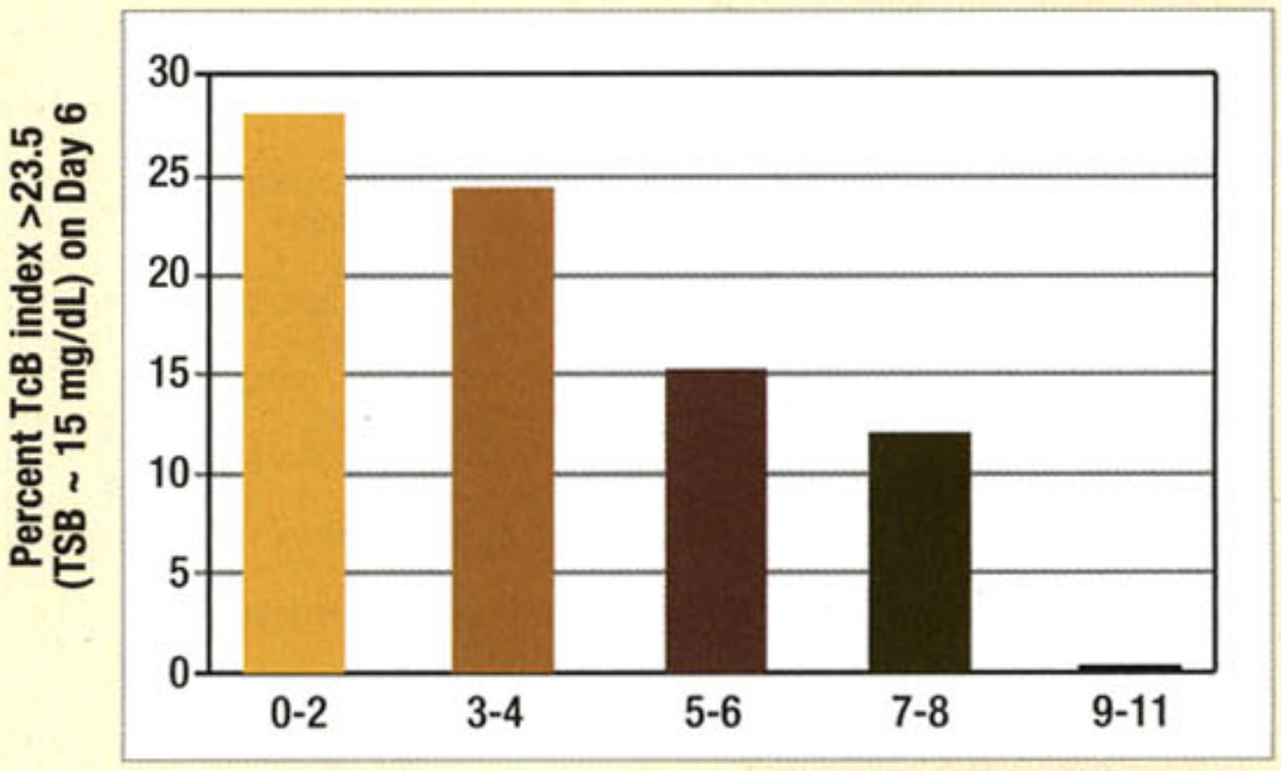
How can hyperbilirubinemia be prevented?

The poor caloric intake associated with inadequate breastfeeding appears to play an important role in the development of severe hyperbilirubinemia.[20,36,37]

FIGURE 2

The more frequent the breastfeeding, the lower the likelihood of hyperbilirubinemia

To gauge the effect of breastfeeding frequency during the first day of life on the bilirubin level, 140 healthy, term, breastfed Japanese newborns, gestational age >37 weeks, were studied. All infants roomed-in with their mother, who recorded the frequency of breastfeeding. TcB measurements were obtained on Day 6 using the original Minolta-Air Shields jaundice meter, which provides a TcB index, not a TSB level. In this population, a TcB index of 23.5 is equivalent to a TSB of 15 mg/dL. The number of infants with TcB indexes >23.5 on Day 6 is shown in relationship to the number of times the mother breastfed her infant in the first 24 hours of life.



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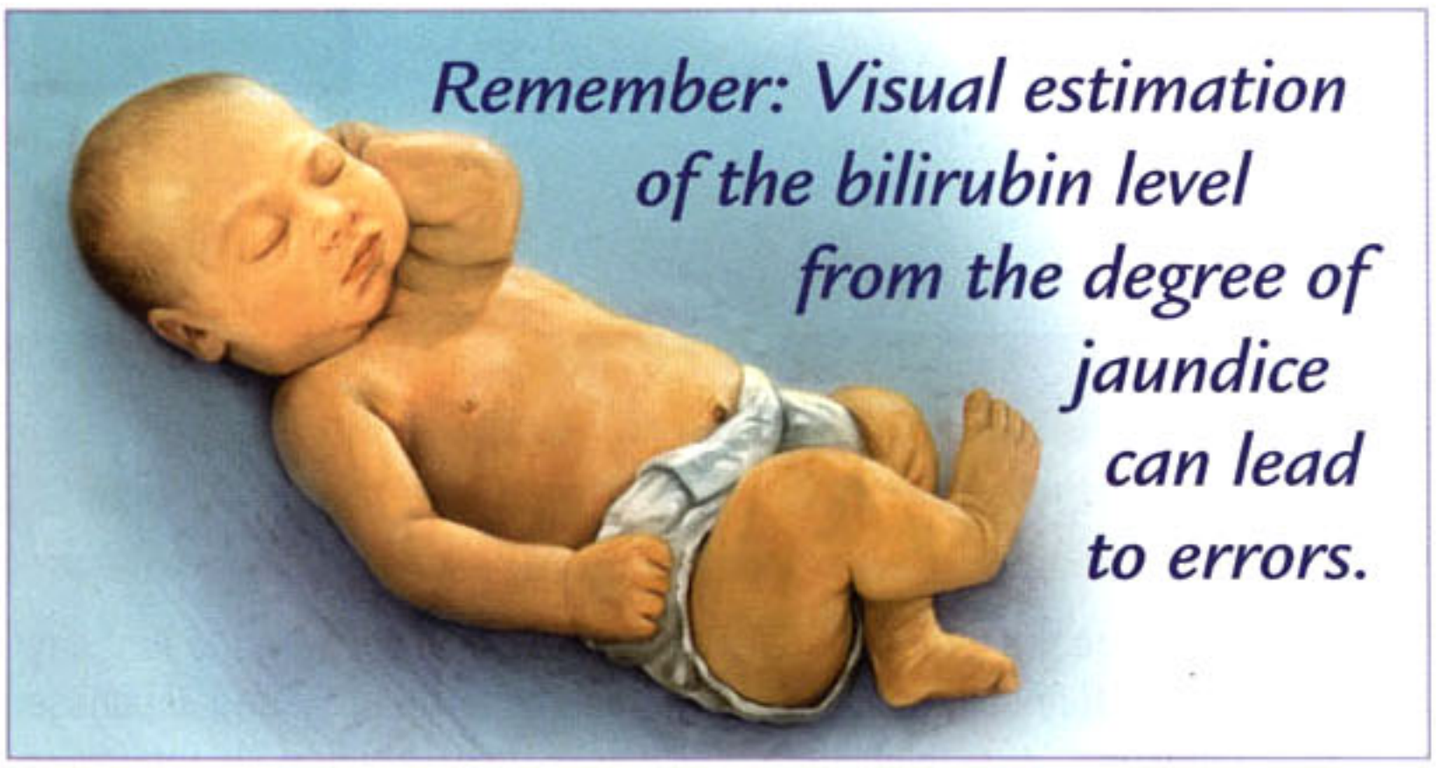
Although exclusive breastfeeding is a well-documented risk factor for dehydration,[38] it is unlikely that dehydration itself is an important cause of hyperbilirubinemia. It is much more likely that caloric deprivation and its effect on the enterohepatic circulation of bilirubin is primarily responsible for severe hyperbilirubinemia.[39]

You need to help mothers breastfeed successfully, and the first step toward achieving successful breastfeeding is to make sure that mothers nurse their infants at least eight to 12 times a day for the first several days. Increasing the frequency of nursing decreases—significantly—the likelihood of hyperbilirubinemia (Figure 2).[40,41]

A breastfed infant who is receiving enough milk should have four to six thoroughly wet diapers in 24

*Direct-reacting bilirubin reacts directly with diazotized sulfanilic acid (i.e., without the addition of an accelerating agent), whereas conjugated bilirubin is bilirubin that has been made water soluble by binding with glucuronic acid in the liver. For clinical purposes, these measurements are interchangeable.



hours and pass three or four stools a day by the fourth day.[42] The stools should have changed from meconium to mustard-yellow, mushy stools by the third or fourth day. Weight loss must also be monitored. Unsupplemented breastfed infants experience their maximum weight loss by the third or fourth day and, on average, lose 6.1% ± 2.5% (SD) of their birth weight.[40,43,44] Infants who lose 10% of birth weight or more require evaluation and close monitoring.

The goal, of course, is to prevent escalation of the TSB level and the potentially serious consequences. Severe hyperbilirubinemia is the focus of Part 2 of this article, which begins on page 41.

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