

Transcutaneous Bilirubin Measurement: Does It Work in the Real World?

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In their study of the routine use of transcutaneous bilirubin (TcB) measurements in 27 well infant nurseries, Taylor et al¹ found that 2.2% of TcB measurements underestimated the clinical laboratory measurement of total serum bilirubin (TSB) by ≥ 3.0 mg/dL, and the tendency for TcB to underestimate TSB increased with advancing newborn age (presumably up to the length of stay of a normal newborn). They nevertheless conclude that TcB measurements “provide reasonably accurate estimates of TSB values” and work well enough as a method for identifying significant hyperbilirubinemia.

Because many nurseries now follow the recommendation to screen all infants with a TSB or TcB before discharge,² it is important to know whether we can rely on the TcB as a screening measurement. Although some 30 years of worldwide experience with this technique have been largely rewarding,³ most of the published data come from research studies where attention is given to detail and quality control. The importance of quality control is illustrated in a report by Wainer et al,⁴ who noted that 25% of the TcB devices they studied “did not perform within allowable limits of our quality control procedures ...” Both of the instruments currently used in the United States are calibrated electronically and not against bilirubin standards. Because the study of Taylor et al¹ more closely incorporates the vagaries of “real world” clinical practice, their finding that only 2.2% of

TcB levels underestimated the TSB by ≥ 3 mg/dL is somewhat reassuring.

Does it matter that in some 2% of infants the TcB was ≥ 3.0 mg/dL lower than the TSB and do we know that this represents an error in TcB measurement? When the TcB and the TSB differ by some clinically relevant amount, it is worth considering whether the gold standard (in this case the TSB) is really gold. Recent attention to calibration techniques and the use of human serum has improved the accuracy of TSB measurements,⁵ but a 2008 American College of Pathologists Neonatal Bilirubin survey revealed that TSBs measured by several established laboratory methods were 2 to 5 mg/dL higher than the reference method.⁵ After concerns expressed by clinicians and laboratory directors, the provider of 1 widely used method, the Vitros (Ortho Clinical Diagnostics, Rochester, NY), which measures conjugated and unconjugated bilirubin by direct spectrophotometry,⁶ made a downward adjustment to their calibrator values. Nevertheless, a 2013 study revealed there was still a mean positive bias of 1.1 mg/dL (12.4%) when the Vitros method was compared with a diazo method (the classic method for measuring the reaction of bilirubin with diazotized sulfanilic acid),⁶ although in 4 of 239 samples there was a positive bias of ≥ 8 mg/dL.⁷ Thus, at least in some cases, what appear to be falsely low TcB levels could be due to erroneously high TSB measurements.

A falsely low (false-negative) TcB measurement could result in failure to

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Opinions expressed in these commentaries are those of the author and not necessarily those of the American Academy of Pediatrics or its Committees.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-3472

DOI: 10.1542/peds.2014-3472

Accepted for publication Nov 5, 2014

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The author has indicated he has no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: Dr Maisels has acted as a consultant for Draeger Medical, Inc.

COMPANION PAPER: A companion to this article can be found on page 224, and online at www.pediatrics.org/cgi/doi/10.1542/peds.2014-1919.

treat an infant who meets the criteria for phototherapy. We use phototherapy to obviate the need for exchange transfusion but currently recommended phototherapy levels in well infants are ~4.5 to 7 mg/dL below exchange transfusion levels,⁸ and there is growing evidence that we are treating too many infants with phototherapy.⁹ Although not extinct, kernicterus in the western world is rare and generally seen only at TSB levels >35 mg/dL.^{10–12} In the absence of sepsis or erythroblastosis fetalis, kernicterus was not seen in Egypt at TSB levels below 30 mg/dL.^{13,14} As the current recommended levels for phototherapy in infants ≥ 35 weeks are at least 10 to 20 mg/dL below these extreme thresholds,⁸ there appears to be ample margin for error. False-negative TcBs can be reduced by setting TcB cut points below the TSB levels that might warrant investigation or treatment.¹⁵ In an outpatient study, where 70 of 118 (59%) of TSBs were ≥15 mg/dL, and 38 (32%) ≥ 17 mg/dL, none of the 33 infants who had a TcB value <14 mg/dL had a TSB value of ≥17 mg/dL (negative predictive value = 1; 95% confidence interval: 0.87–1.0).¹⁶ Thus if we measure the TSB whenever the TcB is ≥13 or 14 mg/dL,^{16,17} the chance of missing the need for phototherapy in a 4-day-old infant is low. Pediatricians in 5 of our affiliated office-based practices and residents in our hospital-based follow-up clinic (ie, nonresearch, real world experience) have been following our recommended TcB cut points¹⁸ for 6 years and we have yet to encounter a significant problem with TcBs.

Because 99% of what is measured by transcutaneous bilirubinometers is the bilirubin in extravascular tissue and not in the blood,¹⁹ TcB measurement is not a substitute for TSB, but it does tell us (1) when to worry about an infant and (2) when we need to obtain a TSB.²⁰ In addition, because it measures bilirubin in tissue, TcB might be

a better predictor of kernicterus than the TSB,²¹ a concept yet to be tested.

TcB measurements work well in both hospital and outpatient settings^{4,16,17} and are better than visual estimation of TSB.^{22–24} Notwithstanding the discrepancies identified by Taylor et al,¹ as long as common sense, clinical judgment, and appropriate follow-up are employed, the likelihood of a bad outcome resulting from an erroneous TcB measurement seems small, whereas the benefits to infants, parents, and care providers of an instantaneous, noninvasive estimate of the TSB level, are abundant.

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A MOLECULAR ARMS RACE: *Physicians have long waged war on bacteria. Unfortunately, despite the plethora of new antibiotics that have been developed over the past 50 years, microorganisms quickly develop resistance. We tend to think of the battle between humans and bacteria in terms of anti-infectives, but this battle permeates many other interactions as well. For example, iron is an essential element for both humans and bacteria. Humans use an evolutionary conserved molecule, transferrin, to transport iron in the body. Transferrin is the major iron transport molecule not only of humans but also of mammals, reptiles, amphibians, and fish. Genetic analysis of humans and closely related species has demonstrated that the genes coding for transferrin have changed dramatically over the past 40 million years. Interestingly, the result is that only one lobe of this two-lobed molecule has changed.*

As reported in The New York Times (Science: December 11, 2014), one reason for the changes may be host responses to bacterial pathogens such as Neisseria. Neisseria requires iron and expresses a surface protein (TbpA) that helps extract iron from transferrin. All the changes in the transferrin molecule have occurred at the binding site of TbpA. In a complementary study, researchers looked at the genes coding TbpA in Haemophilus and Neisseria and discovered that changes occurred only in the regions coding the components that bound directly to transferrin. It would seem that animals have been trying to make it harder and harder for bacteria to steal iron while the bacteria are always evolving new ways to liberate iron from their hosts. The good news is that a new transferrin molecule has emerged that cannot be scavenged by Haemophilus species. The bad news is that bacteria replicate very quickly and it is only a matter of time before they develop a new method to pry iron loose from transferrin.

Noted by WVR, MD

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Pediatrics 2015;135;364

DOI: 10.1542/peds.2014-3472 originally published online January 19, 2015;

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DOI: 10.1542/peds.2014-3472 originally published online January 19, 2015;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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