Serious safety event report

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Overdiagnosis of Newborn Hyperbilirubinemia: A Natural Experiment in Quality Improvement Fundamentals

Kara J. Stirling, MD; Joseph W. Kaempf, MD*; Lian Wang, MS†; Veronica I. Luzzi, PhD, D(ABCC)‡; John V. McDonald, MD§*

Introduction: Two hospitals noted increased newborn hyperbilirubinemia coinciding with an undisclosed total serum bilirubin (TSB) assay change. Clinicians rapidly applied quality improvement methodologies to ascertain increased jaundice evaluations, readmissions, and possible safety issues. **Methods:** In January 2020, 2 hospitals (A and B) transitioned to a new method of measuring TSB using a new clinical chemistry analyzer (Siemens Atellica CH), which measured TSB by vanadate oxidase assay instead of the previous diazo assay. Five affiliated hospitals (C–G) continued to utilize the diazo assay. This natural experiment led to a comparison of data across the 7 hospitals. We analyzed: (1) TSB levels, (2) hospital hyperbilirubinemia readmissions, and (3) paired TSB measurements comparing the diazo assay and vanadate oxidase method. **Results:** Compared to the 2019 baseline, Hospitals A and B had a significant increase in TSBs ≥17.0 mg/dl and TSBs ≥20 mg/dl in 2020; Hospitals C–G did not. Readmissions for phototherapy significantly increased in hospitals A and B in 2020 compared to 2019. Paired blood samples showed bias-elevated TSBs by vanadate assay compared to the diazo method. By 2021, the laboratory resumed processing TSB samples by diazo assay, and the frequency of elevated TSBs and hyperbilirubinemia readmissions returned to 2019 levels. **Conclusions:** Factitious TSB elevation related to an assay change significantly increased newborn hyperbilirubinemia evaluations and phototherapy readmissions. Imbedded quality improvement methodologies of careful structure, process, and outcomes review hastened resolution. *(Pediatr Qual Saf 2023;8:e675; doi: 10.1097/pq9.0000000000000675; Published online August 7, 2023.)*

INTRODUCTION

Newborns in the United States are universally screened for hyperbilirubinemia using transcutaneous bilirubin or total serum bilirubin (TSB). Unlike some historical newborn screening practices, which have not added value over time,[1] screening for hyperbilirubinemia remains critical today. Since 2004, the American Academy of Pediatrics (AAP) has recommended clinical practice guidelines for hyperbilirubinemia management using serial TSB nomograms,[2] with a recent guideline update in 2022.[3] The seminal publication assessing the risk of newborn hyperbilirubinemia utilized the diazo method for TSB measurement.[4] While diazo is the standard method utilized in the United States, there is evidence that alternative assays may provide more consistent TSB results in hemolyzed samples.[5,6] Despite such advantages, results from alternative assays can only be risk-stratified on standard nomograms if there is no bias compared to the standard assay. Even before the 2022 AAP guideline update, widespread utilization of the Bhutani nomogram accompanied by predischarge TSB had nearly eliminated neonatal kernicterus in the United States,[7] highlighting the importance of accurate measurement and standardized guidelines.[8] In addition to infant risk factors, the TSB level at hour-specific ranges for each gestational age provides the practitioner with recommended timing for follow-up. Furthermore, it predicts the infant's likelihood of needing future TSB measurement, examinations, phototherapy, and the rare red blood cell exchange transfusion.

CASE PRESENTATION

A significant increase in the diagnosis of newborn hyperbilirubinemia was observed at 2 hospitals in Portland,

*From the *Women and Children's Institute Providence Health and Services Oregon Portland, Oregon; †Medical Data Research Center, Providence Health & Services Oregon, Portland, Oregon; ‡Tricore Research Institute of Tricore Reference Laboratories, Albuquerque, N.M.; and §Women and Children's Institute (retired) Providence Health and Services Oregon Portland, Oregon.*

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**Corresponding author. Address: Kara J. Stirling, MD, Women and Children's Institute, Providence Health and Services Oregon, 9155 SW Barnes Rd., Portland, Oregon 97225*
PH: 503-282-7002; Fax: 503-280-1290
Email: kara.stirling2@providence.org

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Oregon (A and B) in January 2020, coinciding with the laboratories using a new analyzer to measure newborn TSB samples (Siemens Atellica Solution, Siemens Medical Solutions USA, Inc., Malvern, Pa.). The new analyzer determined bilirubin levels using a vanadate oxidase assay[9]; the previous analyzer had used the standard diazo assay. Five other hospitals (C to G) in the 7 regional hospital system did not change analyzers and continued to use the diazo assay.

Clinicians providing care to newborns were not aware of the assay change. However, they noted increased TSBs and nomogram-defined hyperbilirubinemia in outpatient and inpatient settings. Some institutions have successfully promoted transcutaneous bilirubin use in outpatient settings,[10] but it was not widely available then. Therefore, community practitioners reported increased newborns requiring multiple outpatient blood draws driven by elevated TSBs. In addition, an increase in newborns meeting AAP criteria for outpatient phototherapy resulted in a shortage of phototherapy blankets distributed from outpatient clinics.

Inpatient practitioners concomitantly noted an increase in newborns readmitted to the pediatric ward and neonatal intensive care unit (NICU) with TSB levels triggering nomogram-recommended inpatient phototherapy, including several alarming cases with near exchange transfusion thresholds. Because practitioners were familiar with the fundamentals of quality improvement methodologies and highly reliable organizational principles, they discussed these unusual events by email and at facility-level meetings. Then, they systematically reported their observations at regional newborn and NICU meetings within 2 months of the still unsuspected laboratory assay change at Hospitals A and B (**Table 1**, which describes Providence Health System Oregon Women and Children's NICU and Newborn Quality Improvement Science Infrastructure, **Supplemental Digital Content,** ***http://links.lww.com/PQ9/A509***).

The timing of the increased TSBs also coincided with the beginning of the COVID-19 pandemic, which led to concern that early newborn hospital discharge or limited access to outpatient follow-up might have been contributing factors. However, thorough case reviews of all infants with bilirubin above 20 mg/dL born from January to June 2020 revealed that every mother/newborn dyad received standard inpatient care before birth hospitalization discharge and appropriate outpatient newborn follow-up.

Because practitioners consistently follow AAP hyperbilirubinemia guidelines, the sudden increase in elevated TSBs was perplexing. We queried all TSB samples drawn in the first 14 days of life for all term and preterm infants. Table 1 shows from January to June 2020, Hospitals A and B had a significant increase in TSBs ≥17.0 mg/dl ($P < 0.001$) and TSBs ≥20 mg/dl ($P = 0.01$) compared to the 2019 baseline. All statistical testing was performed using logistic regression. For the bilirubin end points, the regression included an interaction term between the 2 hospital groups and the time to evaluate whether the effects observed from one period to another were different by the group. Also, readmissions for newborn hyperbilirubinemia increased in Hospitals A and B in 2020 compared to 2019 ($P = 0.006$). Hospitals C–G had a nonsignificant decrease in TSBs ≥17.0 mg/dl and a nonsignificant increase in TSBs ≥20 mg/dl in 2020 compared to 2019. Hospitals C–G do not routinely readmit infants for hyperbilirubinemia.

We consulted with regional laboratory services to help ascertain the cause of the increased TSBs. Unknown to the practitioners, Hospitals A and B switched from an analyzer using the diazo assay to the Atellica Solution vanadate oxidase assay in January 2020. We then compared matched blood samples between analyzers and demonstrated a positive bias for the vanadate oxidase assay (Figure 1). The vanadate oxidase assay overestimated TSB compared to the diazo assay with a positive slope bias of 1.13. The positive bias became clinically relevant above 15 mg/dl (Figure 1).

We shared our findings with the analyzer manufacturer, who promptly made an FDA report. Immediate arrangements were made to transition TSBs back to the diazo assay. Initially, newborn blood samples were transported by courier for processing by the diazo method at a different facility. By late 2020, an alternative diazo assay was validated for use in the new analyzer, and by January 2021, newborn TSB samples were once again processed by the diazo method in-house. TSB results from this transition period were not analyzed. In 2021, the levels of newborn hyperbilirubinemia and newborn readmissions for hyperbilirubinemia at Hospitals A and B returned to the previous 2019 baseline (Table 1).

Table 1. Assessment of TSB (Measured in mg/dl) Measurements and Newborn Hyperbilirubinemia Readmissions with or without the Atellica Solution Analyzer (Vanadate Oxidase Assay) Change in 2020

	2019 (January–December)				2020 (January–June)				2021 (January–December)			
Hospital Group	No. of Births	TSB (n) 17–19.9	TSB (n) ≥20	Readmits (n)	No. of Births	TSB (n) 17–19.9	TSB (n) ≥20	Readmits (n)	No. of Births	TSB (n) 17–19.9	TSB (n) ≥20	Readmits (n)
A and B*	6157	2.5% (157)	0.5% (31)	0.9% (54)	2943	4.5% (133)	1.0% (28)	1.5% (45)	6052	3.5% (209)	0.3% (18)	0.8% (47)
C–G†	2280	3.8% (86)	0.3% (6)	N/A	1110	2.3% (25)	0.5% (5)	N/A	2069	2.6% (53)	0.5% (11)	N/A

*Hospitals with the Atellica Solution analyzer (vanadate oxidase assay) change in 2020.
†Hospitals without assay change (ie, used the diazo method throughout 2019–2021).

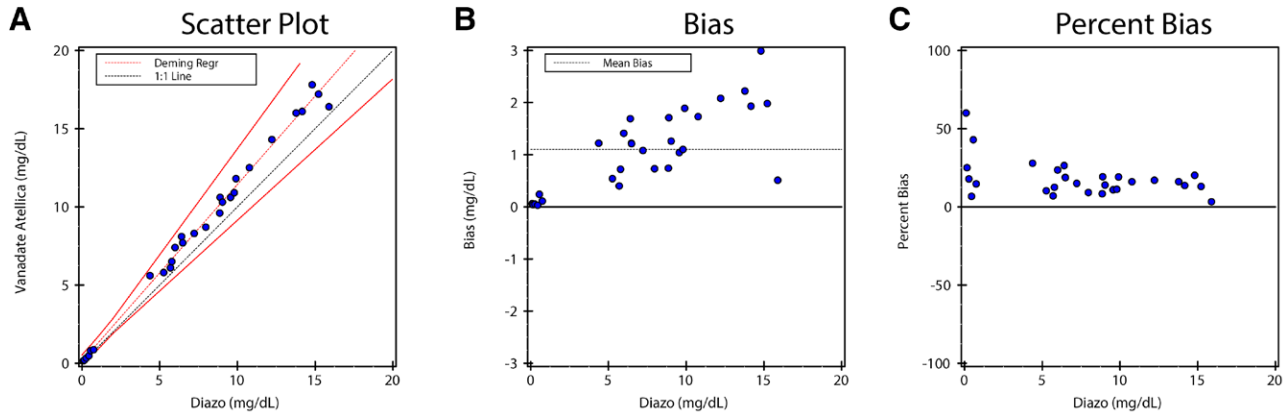

Fig. 1. TSB correlation curves. Data were obtained when the diazo method was reinstated. A, Linear regression comparing the Siemens Atellica vanadate oxidase and diazo methods using serum remnants from newborn specimens. Regression line equation using Demings's regression: y = 1.13 x +0.126. The red lines indicate the regression line and the confidence intervals using the College of American Pathologists' total allowable error (20%). B, Bias comparison using the diazo method as a reference. C, Percent difference graph to demonstrate the vanadate oxidase positive bias.

DISCUSSION

Our pediatric practitioners follow established AAP hyperbilirubinemia guidelines, that is., an evidence-based, standardized protocol that reduces variability, enhances efficiency, and ensures safety by emphasizing proficient detection and prevention strategies. However, introducing a new TSB test assay at 2 of our 7 hospitals correlated with a puzzling increase in TSB measurements, accompanied by a notable escalation in the evaluation and treatment of newborn hyperbilirubinemia. This natural experiment in process and outcomes variability gave us an unintended opportunity to learn and problem-solve using our established quality improvement methodologies. This project addresses an internal process and does not meet the definition of research under the Common Rule. The activity was not research, so 45 CFR 46 did not apply. No IRB review was required.

It is worth noting that appropriate bias comparisons between the 2 assays were performed before the transition, per clinical laboratory regulatory standards. No significant bias for the vanadate oxidase assay was detected. In retrospect, most samples tested had TSB results at the lower end of the concentration range (0–2 mg/dL), which may have limited the ability to detect relevant bias in the higher range clinically important in newborns with jaundice.

Clinicians recognized this technology change as the primary driver of the clinical puzzle by relying upon collaborative communication among nurses, physicians, medical directors, and laboratory personnel across all 7 hospitals. Thankfully, theoretical overutilization was limited to laboratory evaluations, phototherapy, and readmissions. For example, the single infant treated with a red blood cell exchange transfusion from January to June 2020 had a high enough TSB level within the first 24 hours of life that the exchange threshold would have been exceeded even without the positive bias of the vanadate oxidase assay.

CONCLUSIONS

The introduction of a new assay for measuring TSB in the newborn population caused an overdiagnosis of newborn hyperbilirubinemia by clinicians utilizing standard nomograms. However, our imbedded quality improvement culture and highly reliable organizational principles promoted proficient resolution of this unusual occurrence in newborn care and resource utilization: (1) reliable surveillance of diagnostic and utilization metrics, (2) frequent feedback loops between practitioners, (3) collaborative problem-solving between disciplines, and (4) a guideline-driven approach to newborn care that enhances patient safety by promoting proficient standardization of care.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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