Unbound Bilirubin and Risk of Severe Neurodevelopmental Impairment in ELBW Newborns

NICHD
NEONATAL RESEARCH NETWORK

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INTRODUCTION

Background: Unbound bilirubin (**UB**) was measured on day 5±1 in 1101 newborns in the Neonatal Research Network Randomized Controlled Trial of Aggressive vs Conservative Phototherapy (**PT**) in Extremely Low Birthweight Newborns.[1]
UB levels and risk of neurodevelopmental impairment (**NDI**) were significantly higher with conservative PT.

Objective: Quantify the risk of UB exposure for severe NDI (**sNDI**) in surviving ELBW (≤1000 g) newborns

Methods: UB was measured using Arrows (Japan) UB-A1 Analyzers (peroxidase method). Neurodevelopment was assessed at 18 to 22 months corrected age.
In this secondary study, sNDI was defined by any of:

- Score ≤50 on the Bayley II Mental or Psychomotor Developmental Index
- Score of 5 on the gross motor function (movement requires adult assistance)
- Severe bilateral hearing loss

* UB values were standardized between laboratories as Z-score percentiles (**%tiles**)
* Risk of UB exposure for sNDI was estimated using logistic regression[2] (**LR**) and ensemble learning targeted maximum likelihood estimation (**ELTMLE**)[3]
* Adjusted estimates controlled for baseline variables: gestational age (**GA**), small-for-GA (**SGA**), sex, multiple birth, antenatal steroid use, outborn, severe IVH, maternal education, insurance type, clinical stability at blood sampling, and perinatal center; ELTMLE included PT regimen (aggressive vs conservative) for the propensity score exposure model

RESULTS

825 infants survived and completed evaluations allowing assignment of sNDI status: mean GA 26.5±1.8 wk; birthweight 795±131 g

The correlation of UB and total bilirubin (**TB**) from the same blood sample was poor: R^2=0.24

There was a sharp increase in risk of sNDI at the 85th %tile of UB Z-scores (**Figure 1**).

- We could not specify a precise UB concentration at the 85th %tile due to interlaboratory variation

Figure 1. Risk of Severe NDI by Percentile of UB Z-score

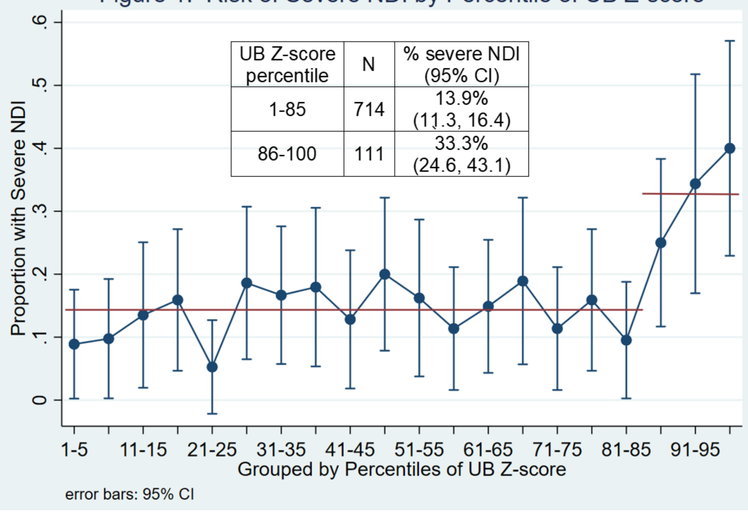

Table 1 Risk of sNDI	N	Crude Risk	Adjusted Risk Logistic	Adjusted Risk ELTMLE
UB Z-score ≤85th %tile	714	13.9%	14.5%	14.4%
UB Z-score >85th %tile	111	33.3%	27.0%	27.6%
Risk Difference (Increased Risk) (95% CI)		19.5%	**12.5%** (1.7, 23.3) P=0.02	**13.3%** (9.3, 17.3) P<0.001
Risk Ratio (Increased Risk) (95% CI)	2.40		**1.86** (1.2, 2.8) P=0.003	**1.88** (1.5, 2.4) P<0.001

The point estimates for increased risk at >85th %tile were similar with ELTMLE (13.3%) and LR (12.5%), but the 95% confidence intervals (CIs) were narrower with ELTMLE: 9.3, 17.3% vs 1.7, 23.3% (**Table 1**)

CONCLUSIONS

- In ELBW newborns a single elevated UB level at age 5±1 days was associated with a large increase in risk of severe NDI
- TB is a poor substitute for UB in ELBWs
- Prospective studies to validate UB risk thresholds and randomized trials to evaluate clinical utility should have a high priority

References
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2. Norton E. et al. Computing adjusted risk ratios and risk differences in Stata. *The Stata Journal* 2013 13(3): 492–09.
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