

Title: Dose-Response Relationship Between Parenteral Nutrition Exposure And Direct Hyperbilirubinemia In Infants <1500 Grams At Birth

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Background: A variety of clinical factors have been associated with development of conjugated hyperbilirubinemia (CH) in very low birth weight (VLBW, <1500 g at birth) infants.

Objective: To identify potentially modifiable risk factors for the development of CH in VLBW infants.

Design/Methods: We examined clinical databases and medical records for all VLBW infants born 2000-2005, admitted  $\leq 2$  days (d) of age, and treated for  $\geq 7$  d at a single center. Data were collected regarding infant characteristics, medical course, and nutritional therapy. Univariate and multivariate analyses were used to identify factors associated with CH (conjugated bilirubin  $\geq 2$  mg/dl).

Results: Inclusion criteria were met by 348 infants, of whom 78 developed CH with mean $\pm$ SD peak conjugated bilirubin 5.5 $\pm$ 3.4 mg/dl. Annual incidence varied from 15%-35%. Infants with vs without CH had significantly ( $p < .05$ ) lower birth weights (925 $\pm$ 242 vs 1137 $\pm$ 264 g), more exposure to parenteral nutrition (PN) (42 $\pm$ 22 vs 21 $\pm$ 12 d) and mechanical ventilator (17 $\pm$ 26 vs 6 $\pm$ 10 d), and more intraventricular hemorrhage grade 3/4 (9% vs 3%) and necrotizing enterocolitis in the 1st 21 d of life (6% vs 1%). There was no detected difference in incidence of SGA or fungal or bacterial infection in the 1st 21 d of life. In multivariate analysis, only number of d PN was associated with CH. Odds of CH increased 5% per day PN exposure, and increased five-fold with  $>20$  d PN exposure (Figure). ROC curve area using PN d as the sole predictor of CH was 0.82. For infants with CH, peak bilirubin correlated with d PN exposure ( $p < .001$ ).

Conclusions: This cohort showed a direct relationship between PN exposure and incidence and severity of CH that outweighed all other tested risk factors. Further research is needed to identify PN components associated with CH and reduce PN-related compromise in liver function.

