CHOLESTASIS ALTERS THE MATURATION OF THE EXTREMELY PRETERM NEONATAL GUT MICROBIOME

Lauren E. Lynch[1], Amy B. Hair[2], Heeju Yang[3], Laura A. Gollins[3], Geoffrey A. Preidis[4]

[1] Baylor College of Medicine, Department of Pediatrics, Gastroenterology, Hepatology & Nutrition

[2] Baylor College of Medicine, Pediatrics, Neonatology

[3] Texas Children's Hospital, Pediatrics, Neonatology

[4] Baylor College of Medicine, Pediatrics, Gastroenterology, Hepatology & Nutrition

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Background: Cholestasis (impaired bile flow from the liver to the intestine) affects ~1:2500 births, causes poor neonatal growth, and may progress to liver failure and death. Underlying causes of most cases are unknown. Normal bile flow requires an intact liver-gut-microbiome axis that contains bile salts. Liver-derived primary bile salts are transformed into secondary bile salts by microbial bile salt hydrolase (BSH) enzymes. In turn, bile salts shape gut microbiota composition and function. How the liver-gut-microbiome axis develops over time in preterm newborns, and whether cholestasis alters this development, is unknown. We aimed to test the hypotheses that: 1) The gut microbiome of extremely premature neonates without cholestasis contains BSH genes and develops in a predictable manner over time; 2) Cholestasis interrupts this normal pattern of development.

Materials/Methods: In this single-center study, 24 extremely preterm infants < 1500 grams birthweight born at Texas Children's Hospital were enrolled. A subset of infants with cholestasis (n=12, mean peak conjugated bilirubin of 4.3 mg/dL) were compared to age matched controls without cholestasis (n=12). Weekly stool samples were collected throughout hospitalization and analyzed by whole metagenomic sequencing.

Results: Principal coordinate analysis revealed that gut microbiota from extremely preterm neonates without cholestasis develop in a predictable manner over time ($P<0.0001$, Figure). Pathway analysis identified increasing secondary bile salt biosynthesis as the most distinctive metagenomic feature of preterm development ($P<0.00001$). Control neonates also had increasing abundance of BSH genes ($P<0.05$) and of the BSH carrier Clostridium perfringens ($P<0.001$). Strikingly, these developmental signatures were completely absent in cholestasis. Instead, cholestasis increased microbial community diversity without increasing BSH genes or C. perfringens. Compared to controls, cholestatic neonates required more days of parenteral nutrition and antibiotics. Cholestatic infants exhibited poor neonatal growth, indicated by lower head circumference and weight velocities.

Conclusions: We identified a pattern of development of the extremely preterm neonatal gut microbiome that is interrupted by cholestasis. Increased gut microbiota diversity in cholestasis may reflect lack of bile salts in the intestine. Ongoing studies are exploring the liver-gut-microbiome axis as a therapeutic target to enhance neonatal growth.

Images / Graph / Table

Gut microbiome development in extremely preterm neonates is disrupted by cholestasis