Neonatal Gut Microbiota Alterations and Local Inflammation Induced by Escherichia coli Infection are Modified by Lactobacillus rhamnosus Prophylaxis

Susana Chavez-Bueno
Hao Xuan
Shahid Umar
Concong Zhong
Wei Yu

See next page for additional authors

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Creators
Susana Chavez-Bueno, Hao Xuan, Shahid Umar, Concong Zhong, Wei Yu, and Venkatesh Sampath
Neonatal Gut Microbiota Alterations and Local Inflammation Induced by *Escherichia coli* Infection are Modified by *Lactobacillus rhamnosus* Prophylaxis

Hao Xuan, PhD; Shahid Umar PhD; Cuncong Zhong, PhD; Wei Yu, PhD; Venkatesh Sampath MD; Susana Chavez-Bueno, MD

Presenter Name: Susana Chavez-Bueno, MD
Institution: Children’s Mercy Hospital and Univ. of Missouri School of Medicine, Kansas City.
Email: schavezbueno@cmh.edu
Susana Chavez-Bueno, MD
Has documented no financial relationships to disclose or Conflicts of Interest (COIs) to resolve.
Susana Chavez-Bueno, MD has documented this presentation will not involve discussion of unapproved or off-label, experimental or investigational use.
Background

- *Escherichia coli* is the most common Gram-negative causing neonatal sepsis

- Among premature newborns, *E. coli* is the predominant cause of sepsis in the first week of life (Schrag, Farley et al. 2016)

- Rates of *E. coli* early-onset sepsis are as high as 7-10 cases per 1,000 live births in VLBW infants, and continue to increase (Mukhopadhyay and Puopolo, 2017) (Stoll and Puopolo, 2020)
Ingestion of *E. coli* by newborn animals causes bacteremia

*E. coli* invades intestinal epithelium and translocates into the bloodstream

Intestinal invasion by *E. coli* produces local inflammation, apoptosis, and increased intestinal permeability

There are no preventive measures against *E. coli* early-onset sepsis
Background

- Probiotics modify the intestinal microbiota and modulate the inflammatory response to pathogenic gut bacteria (Plaza-Diaz, Ruiz-Ojeda et al. 2018)

- Probiotic supplementation reduces the risk of late-onset sepsis in preterm infants (Rao et al., Pediatrics, 2016)

- Probiotics decreased gut translocation of *E. coli* in newborn rats (Zeng, He et al. 2017)

- Probiotics have a protective effect, however, the mechanisms involved in preventing intestinal translocation and neonatal bacteremia are not well-understood
Objective

To determine the effects of *Lactobacillus* on the intestinal microbiota and inflammation in neonatal rats orally infected with *E. coli*. 
**Methods**

- *Lactobacillus rhamnosus GG* (**LGG**) (ATCC 53103) is a probiotic strain widely used in humans worldwide (Doron, Snydman et al. 2005)

- *E. coli* strain **SCB34** is a well-characterized, highly invasive neonatal clinical isolate that produces bacteremia by oral inoculation (Chavez-Bueno et al. 2014)

**Experimental groups:**

1) LGG → SCB34 infection
2) Phosphate buffered saline (PBS) → SCB34 infection
3) LGG → PBS
4) PBS → PBS

- Day 1: Pretreatment x2
- Day 2: Pretreatment X2 + Infection
- Day 7: Sample collection
Methods

- On day 7 p.i., distal colon with stool were collected for 16S ribosomal RNA sequencing using Illumina technology.
- AbundantOTU+ was used to generate de novo operational taxonomic units (OTUs).
- Observed, ACE, Shannon, and Simpson indices were used for alpha diversity.
- Bray-Curtis and Jaccard indices were used for beta diversity.
- Linear discriminant analysis effect size (LEfSe) was used to determine differences at the genus level.
- Expression of ICAM-1, GRO-1, Toll-like receptor 4 (TLR4), and Single-Immunoglobulin Interleukin-1 Related Receptor (SIGIRR) was measured in ileal homogenates by real-time PCR.
Results

Distinct taxonomic distribution of intestinal microbiota samples according to treatment group
Alpha Diversity is Greater in *E. coli*-infected Groups
Alpha Diversity is Greater in *E. coli*-infected Groups
Beta-Diversity Analyses

Bray-Curtis Index

Jaccard Index
LEfSe Analyses for *Lactobacillus* and *Escherichia* Genera
LEfSe Analyses for Anaerobic Bacteria

- **Clostridium_sensu_stricto_1**
  - Filtered Count
  - Log-transformed Count

- **Romboutsia**
  - Filtered Count
  - Log-transformed Count

- **Veillonella**
  - Filtered Count
  - Log-transformed Count

Legend:
- PBS-PBS
- Lac-PBS
- PBS-SCB34
- Lac-SCB34
LGG Pretreatment Significantly Decreases Intestinal Inflammation

ICAM1
- PBS-PBS: ns
- PBS-SCB34: p=0.0293
- Lacto-SCB34: p=0.0455

GRO-1
- PBS-PBS: p=0.0054
- PBS-SCB34: p=0.039

TLR4
- PBS-PBS: p=0.0054
- PBS-SCB34: p=0.0075

SIGIRR
- PBS-PBS: p=0.036

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Conclusions

- *Lactobacillus* GG pretreatment significantly modified clinically relevant microbiota features of neonatal pups orally infected with *E. coli*
- LGG pretreatment attenuated *E. coli*-induced intestinal inflammation
- Future studies will further characterize the observed changes in the *Escherichia* intestinal microbiota populations at the species level, and on the mechanisms by which probiotics modify various anaerobic genera in the neonatal gut
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Children's Mercy Hospital

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