Neonatal Virome in Culture-Negative Sepsis & Systemic Inflammation in Preterm Neonates

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BACKGROUND

- Neonatal sepsis is a leading cause of infant morbidity and mortality, often presenting with non-specific signs and symptoms.
- "*Culture-negative sepsis*" – symptomatic and treated with antibiotics, but blood cultures are negative.
- Circulating blood microbiome in healthy adults and non-infective disease states is reported
- Perturbations to the abundance, composition, and/or function of the microbiome has been implicated in various diseases.
- No data on the virome in preterm infants and its role in neonatal sepsis.

OBJECTIVES

1. Determine the diversity and composition of the virome in preterm neonates who are suspected to have clinical sepsis

2. Determine the association of the virome signatures with systemic inflammation and neonatal outcomes

HYPOTHESES

- **Hypothesis 1:** Preterm infants with clinical sepsis will have distinct virome signatures (viral DNA composition, abundance, and/or diversity) compared to those without sepsis.

- **Hypothesis 2:** Increased viral DNA load, diversity, and/or relative abundance will positively correlate with pro-inflammatory cytokines in the serum that lead to tissue inflammatory injury.

METHODOLOGY

- **Study design:** Prospective cohort study

- **Population:** Preterm infants born <37 weeks gestation undergoing a late-onset sepsis evaluation in the NICU (**Fig. 1**)

- **Sample collections: S**tool, nasopharyngeal and skin swabs along with blood samples at the time of sepsis evaluation, prior to antibiotic administration.

- **Outcome:** Virome evaluation in preterm neonates by virome capture sequencing methods established at the CMMR laboratory. Serum cytokine profiles will be evaluated at the Proteomics core lab.

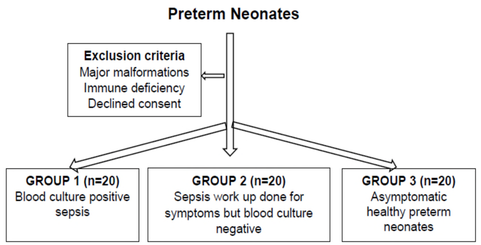

Figure 1: The sample size of 20 patients per group will provide 80% statistical power to detect an effect size of 1.00 at the 5% significance level.

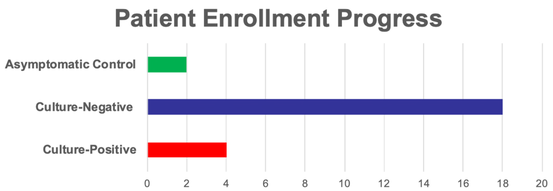

Figure 2: Overall 44 patients enrolled, 22 subjects underwent a sepsis evaluation from which 4 were positive and 18 negative. 2 patients enrolled in control arm.

PRELIMINARY DATA

- Neonates with CLABSI (infected) were compared with those without CLABSI (uninfected).
- Significant decrease in alpha diversity and operational taxonomic units (OTUs) of the blood microbiome in CLABSI neonates vs. uninfected neonates (**Fig. 3**).
- The blood microbiome showed a significant decrease of *Acinetobacter* (p=0.023) and *Faecalibacterium* (p=0.048) at the level of the genus but no differences at the phylum level (**Fig. 4**).
- Presence of a blood microbiome in all neonates even in those without infection.

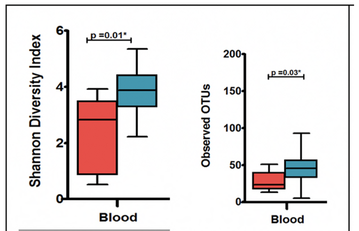

Figure 3: Significant decrease in Shannon diversity index and observed OTUs in the blood microbiome of patients with CLABSI (Infected) compared to those who did not (uninfected)

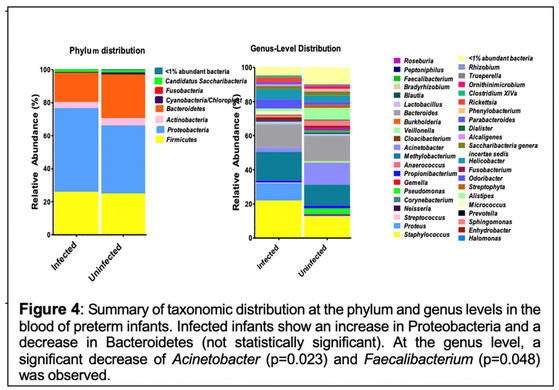

Figure 4: Summary of taxonomic distribution at the phylum and genus levels in the blood of preterm infants. Infected infants show an increase in Proteobacteria and a decrease in Bacteroidetes (not statistically significant). At the genus level, a significant decrease of *Acinetobacter* (p=0.023) and *Faecalibacterium* (p=0.048) was observed.

ANTICIPATED RESULTS

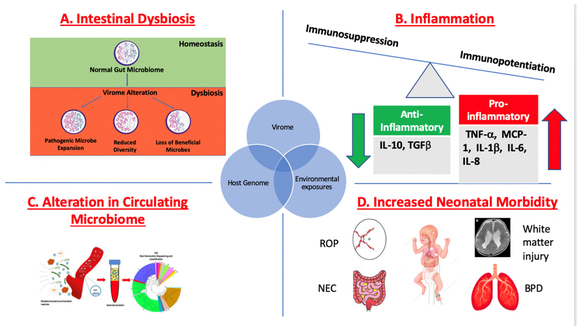

Figure 5: Predicted Outcome of Virome Alteration in Culture-Negative Sepsis. 1. Neonatal virome will likely correlate with intestinal dysbiosis (A) as marked by increased pathogenic gut microbes, decreased diversity or loss of beneficial microbes. 2. Virome alteration in patients with clinical sepsis will likely correlate with pro-inflammatory cytokine reaction (B); alteration of the circulating bloodstream microbiome (C); as well as correlate with increased neonatal morbidity and mortality (D).

CONCLUSIONS

This pilot research study is currently underway and will potentially underpin the pathophysiology of culture-negative sepsis in relation to the virome and systemic inflammation.

REFERENCES

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