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Dysbiosis of Gut Microbiome in Neonatal Sepsis - A Prospective Study

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ABSTRACT

Background information: Sepsis is a life-threatening condition, and sepsis in newborn babies is called neonatal sepsis. The highest rate of sepsis among newborns is found in India. The gut microbiome is crucial to maintaining health and the development of disease. So, the study aims to analyze the gut microbiome of infants with neonatal sepsis.

Methodology: Three faecal samples were collected from neonates with clinical signs and symptoms of sepsis and processed. Metagenomic DNA was extracted using a Qiagen stool DNA extraction kit. Amplification of the bacterial 16SV3-V4 region was carried out. 16S Microbiome Profiling was performed. Cluster Generation and Sequencing were done. Bioinformatics analysis was performed to process the data of the samples. A comparative study of the samples was conducted at different taxonomic levels.

Results: Most abundant species in the samples were identified as unclassified species from the genus *Enterococcus* (40.18%), unclassified species from the genus *Streptococcus* (32.66%) and unclassified species from the family *Enterobacteriaceae* (15.17%), respectively. The results correlated with blood culture findings.

Conclusion: The genera of the causative organism in neonatal sepsis correlate to the most prevalent bacteria in the gut microbiome. Sepsis may be due to a gut-derived bacterial translocation phenomenon and requires novel strategies for prevention.

Keywords: *Neonatal sepsis, Gut microbiome, 16S Microbiome Profiling, Bioinformatics analysis, taxonomic levels and bacterial translocation*

1. INTRODUCTION

Sepsis is a life-threatening condition, and sepsis in newborn babies is called neonatal sepsis. It is the frequent cause of newborn mortality and accounts for nearly 50% of all neonatal fatalities in underdeveloped nations.[1] Clinical features vary from nonspecific symptoms to specific symptoms. It can be classified into two major categories - Early onset sepsis (EOS) and late onset sepsis (LOS).[2]

The study of the gut microbiome's origins in neonates, in particular, has become one of the most fascinating subtopics in genomics. The gut microbiome is crucial to maintaining health and the development of disease.[3] *Actinobacteria* and *Bacteroidetes* primarily colonize the full-term infant gut microbiome during the first week of life.[4] Healthy gut shows enhanced alpha microbial diversity. Healthy gut microbiota has the potential to prevent bacterial translocation.[5]

During and immediately after birth, these newborns' intestines are colonized with facultative anaerobic bacteria.

Bifidobacterium becomes the most common genera linked with a healthy gut in early life.[6] *Bifidobacteria* have been demonstrated to have immunomodulatory properties and the ability to defend against infections and enhance barrier function.[7]

Researchers have been able to identify the microbiome in neonatal sepsis using next-generation sequencing technology, providing new perspectives into disease pathogenesis.[8] This study was attempted to analyze the gut microbiome of infants with neonatal sepsis

2. MATERIALS AND METHODS

The prospective study was conducted in Chettinad Academy of Research and Education (CARE), Chettinad Hospital and Research Institute (CHRI). The study was conducted after obtaining Institutional Ethics Committee approval. The study comprised neonates (<28 days old) of both sexes who showed symptoms of neonatal sepsis. Temperature instability, abdominal distension, food intolerance, tachycardia (HR>190bpmin), bradycardia (HR>90bpmin), dyspnea, tachypnea (>70/min), hepatosplenomegaly and irritability are the signs and symptoms of sepsis. Clinical signs and symptoms and laboratory findings such as CBC, CRP and/or blood cultures are used to diagnose neonatal sepsis in the study setting.

Three neonates were chosen based on the clinical signs and symptoms, and the stool samples were collected for gut microbiome analysis. Samples 1 and 2 were collected from early preterm and late preterm neonates delivered by caesarean section, respectively. Sample 3 was collected from a full-term neonate delivered by vaginal birth.

2.1 Metagenomic DNA extraction and generation of the first amplicon

DNA was extracted using a Qiagen stool DNA extraction kit. The quality of DNA was evaluated on a spectrophotometer by assessing the A260/280 ratio.

The extracted metagenomic DNA and bacterial 16S V3-V4 region-specific primer set were used to set up the PCR. (Table 1) Agarose gel (1.25%) was used to resolve 3 µl of PCR product at 120V for 60 min and is shown in figure 1.

Fig.1. QC of first amplicons

Note: Lane 1: Ladder, Lane 2,3 &4 – PCR amplified product

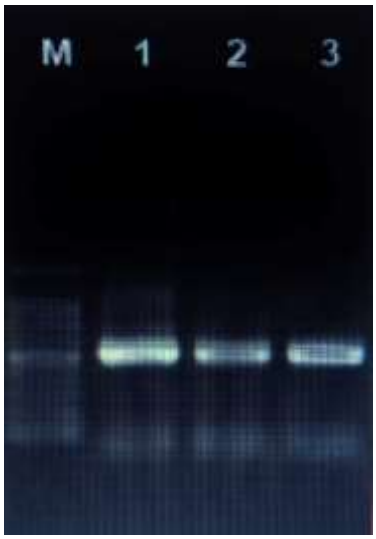


Table 1: Primers used for amplification

16S rRNA F	**GCCTACGGGNGGCWGCAG**
16S rRNA R	**ACTACHVGGGTATCTAATCC**

2.2 Preparation of 2 x 300 MiSeq library

Using the Nextera XT Index Kit and 16S Metagenomic Sequencing Library preparation methodology, the amplicon library was created. The samples that passed QC were then prepared for the first amplicon synthesis and Nextera XT Index Kit-based NGS library construction. On the Illumina MiSeq platform, libraries were sequenced using 2 x 300 bp chemistry to produce 1.0 lakh reads.

2.3 Library quantity and quality control (QC) on Agilent 4200 Tape Station

The amplified library was evaluated using D1000 Screen tape and a 4200 Tape Station system. (Table 2)

Table 2: Tape-Station profile of the library

Sample	From [bp]	To [bp]	Average Size[bp]	Conc. [ng/µl]	RegionMolarity [nmol/l]	Total Percentage
1	463	864	611	8.53	21.7	85.17
2	475	740	592	8.95	23.4	85.57
3	457	787	590	13.3	34.8	84.63

2.4 Cluster Generation and Sequencing

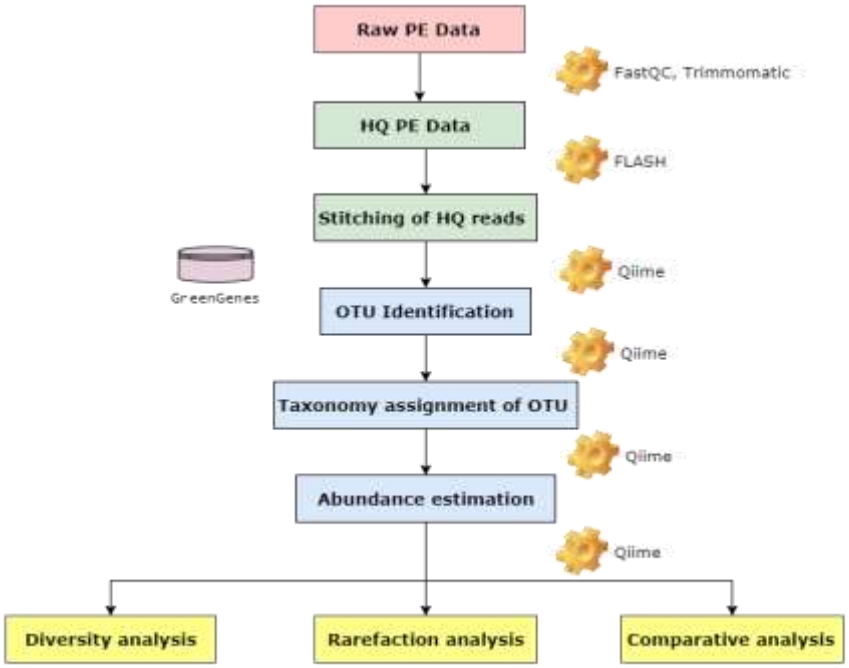
After establishing the mean peak size from the Tape Station profile, libraries were added onto MiSeq at the proper concentration (10–20 pM) for cluster formation and sequencing.

2.5 Bioinformatics analysis

Fast Tree, a technique for heuristic-based maximum-likelihood phylogeny inference, and the Ribosomal Database Project (RDP) classifier, which uses a naive Bayesian classifier to assign taxonomic data, are two examples of the tools and algorithms that constitute QIIME, comprehensive software. As a result, QIIME can incorporate new independent techniques very quickly and easily.

To process the data of three 16S samples, the following steps were involved (Figure 2):

Fig.2. Bioinformatics workflow



- Adaptor sequences, low-quality sequences and ambiguous reads were removed using Trimmomatic v0.38 to provide high-quality clean reads with a sliding window of 10 bp and a minimum length of 100 bp.

- Combining the single-end reads with the PE data was done
- Selecting OTUs (Operational Taxonomic Units) based on sequence homology in the reads and selecting a typical 16S rRNA sequence for each OTU using the Green genes database was done.
- Using reference databases, a taxonomic identity is assigned to the OTU.
- Diversity measures were calculated for each sample.

OTU-picking detects strikingly similar sequences throughout the sample and provides a framework for comparing community structure. Based on their degree of sequence similarity, all the sequences were grouped into OTUs. OTUs are collections of sequences that are usually created using UCLUST at 97% sequence similarity to reflect some degree of taxonomic relatedness. Each cluster denotes a species. Each OTU consists of several sequences; one typical OTU sequence has been chosen for further investigation. The representative sequence was utilized to identify the OTU's taxonomic group. This result is shown in the chart figures at individual taxonomical levels.

3. RESULTS

3.1. 16S amplicon analysis

Libraries were sequenced and produced more than 1.0 lakh reads (Table 3) .

Table 3: High-Quality read statistic

Sample ID	Raw reads	Raw total bases	Raw data in Mb	HQ reads	HQ total bases	HQ data in Mb
Sample 1	1,72,304	103,727,008	103.73	1,40,135	76,672,613	76.67
Sample 2	1,75,502	105,652,204	105.65	1,41,787	75,235,586	75.24
Sample 3	1,96,202	118,113,604	118.11	1,66,218	89,629,772	89.63

3.2 Alpha diversity

Alpha diversity uses a single value to indicate the diversity of the microorganisms in the sample. The distribution of the species-level annotations can be used to determine the alpha diversity of samples. Sample 1 had a high level of alpha diversity (3.00 – 3.49). Samples 2 and 3 had very high alpha diversity (3.50 and above) **(Table 4).**

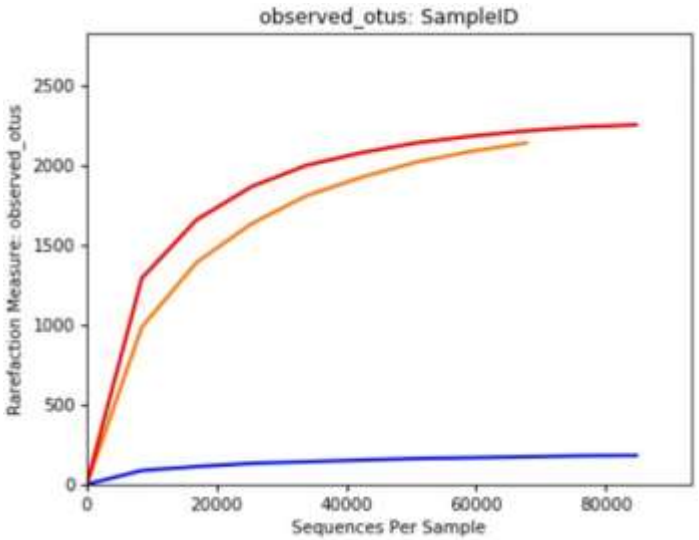
Table 4: Alpha Diversity

SI No	Sample Name	Observed OTUs	Shannon alpha diversity
1	**Sample 1**	**188**	**3.32**
2	**Sample 2**	**2,170**	**6.14**
3	**Sample 3**	**2,259**	**8.01**

3.3 Rarefaction curve

Rarefaction gives the estimation of the species richness of the samples. The vertical axis represents the diversity of the community, and the horizontal axis displays the total number of sequences used in the diversity computation. **(Fig.3)**

Fig.3. Rarefaction plot



Note: Sample 1 Sample 2 Sample 3

Rarefaction curve analysis showed that all three samples had nearly 60000 to 80000 sequences. It shows the overall diversity of a metagenome by combining the number of sequences and their relative abundance. Sample 1 has 188 OTU's indicating low species diversity whereas samples 2 and 3 had 2170, 2259 OUT's respectively, indicating high species diversity of a metagenome.

3.4 Krona Charts

Multi-layered pie charts, or krona plots, allow hierarchical data to be visualized at various levels. The plots can be zoomed in or out to check the abundance at any desired taxonomic level. (**Fig.4-6)**

Fig.4. Krona chart of Sample 1

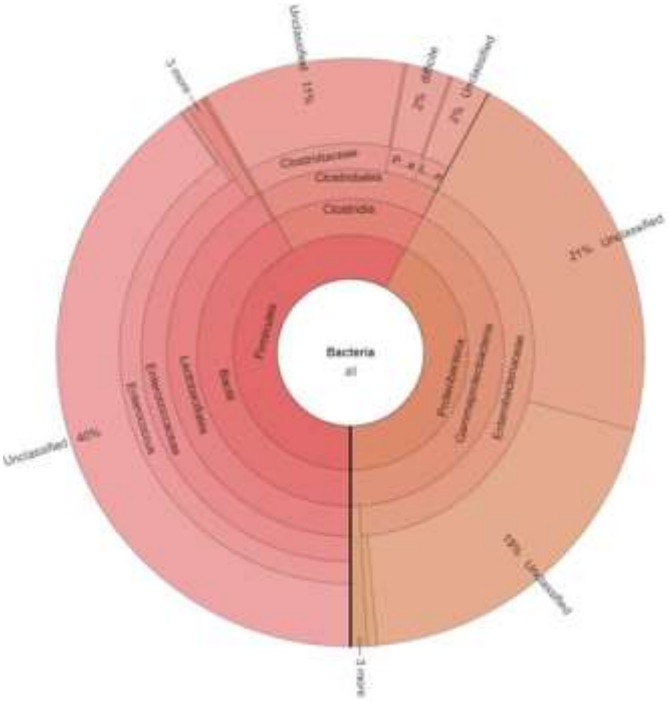


Fig.5. Krona chart of Sample 2

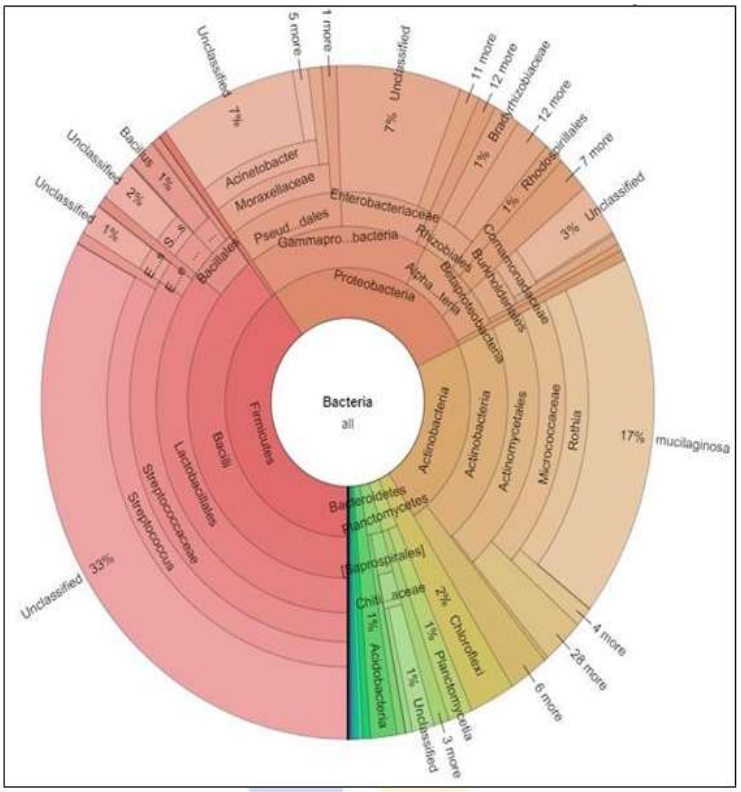
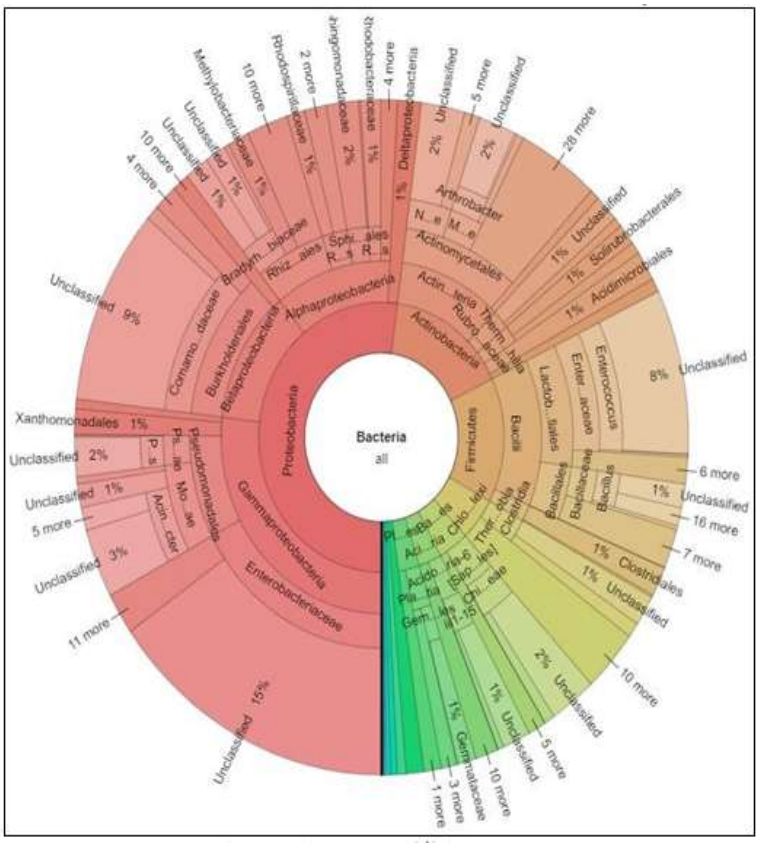


Fig.6. Krona chart of Sample 3



Correlation with blood culture report

- *Enterococcus faecalis* was identified in the blood culture report from sample 1. *Streptococcus viridans* and *Escherichia coli* were identified from samples 2 and 3.
- All three samples had a concordance of bacterial strains isolated from blood culture.
- The genera of the causative organism in NS correlate to the prevalent bacteria in the gut microbiome before diagnosis. During diagnosis, the organism detected by conventional blood culture was the most common OTU in the gut microbial flora.

4. DISCUSSION

Phylum level

In our study, *Firmicutes*, followed by *Proteobacteria*, were relatively abundant in samples 1 and 2, and the most abundant phyla in sample 3 was *Proteobacteria.* It was similar to a study by Stewart *et al.,* 2017 and Cuna *et al.,* 2021. Both studies stated that neonates who had sepsis were shown to have reduced levels of *Bifidobacteria* and higher levels of *Proteobacteria.*[9,10] Ficara M *et al.,* 2020, showed *Bifidobacterium* colonization in premature newborns has been delayed. Preterm births that occur before 33 weeks of gestation appear to hinder *bifidobacterial* colonization and put preterm infants at risk of illnesses[11]. Cuna *et al.,* 2021 stated that the microbiota of preterm infants exhibits differences from term infants in terms of delayed colonization, fewer bacterial species, and lower diversity and abundance[10].

Class Level

The most abundant class in sample 1 and sample 3 were *Gamma proteobacteria.* It was similar to a study by Ho TT *et al.,* 2018. They stated that higher levels of *Gamma proteobacteria* increase the risk of developing intestinal dysbiosis. [12] In sample 2, *Firmicutes* bacilli was the predominant class. It was similar to a study conducted by Selma-Royo M *et al.,* 2021. [13]

Table 5: Most abundant taxonomic units

Sample / Taxonomic units	Sample 1 (%)	Sample 2 (%)	Sample 3 (%)
Phylum	**Firmicutes (57.81)**	**Firmicutes (39.69)**	**Proteobacteria (51.80)**
Class	**Gammaproteobacteria (42.14)**	**Firimicutes Bacilli (39.29)**	**Gammaproteobacteria (26.67)**
Order	**Lactobacillales (41.58)**	**Lactobacillales (35.29)**	**Enterobacteriales (17.15)**
Family	**Enterobacteriaceae (41.28)**	**Streptococcaceae (32.26)**	**Enterobacteriaceae (17.15)**
Genus	***Enterococcus* (40.28)**	***Streptococcus* (32.68)**	**Unclassified genus from the family Enterobacteriaceae (15.17)**
Species	**Unclassified species from genus *Enterococcus* (40.18)**	**Unclassified species from genus *Streptococcus* (32.66)**	**Unclassified species from the family Enterobacteriaceae (15.17)**

Order level

Lactobacillales were relatively abundant in order found in samples 1 and 2 (41.6% & 35.3%). *Enterobacteriales* (17.1%) was the most common order in sample 3. It was similar to a study done by Akagawa S *et al.,* 2019. They stated that *Bacillales* and *Lactobacillales* were highly represented in newborns delivered by caesarean section, but Bacteroidales and Enterobacteriales were highly represented in neonates delivered vaginally[14].

Family level

Enterobacteriaceae and *Enterococcaceae family* were relatively abundant in sample 1 (41.3% & 40.6% respectively). It was similar to a study by Akagawa S *et al.,* 2021, who found that *Enterococcaceae* were relatively high at the family level in infected neonates.[15]

*The Streptococcaceae f*amily was predominantly found in sample 2 (33.3%). It was similar to a study by Sitarik AR *et al.,* 2017. They showed the increased abundance of *Ruminococcaceae and Streptococcaceae*.[16]

Enterobacteriaceae family was predominant in sample 3 (17%). It concurred with a study conducted by Sanidad KZ *et al.,* 2020. [17] They stated that after birth, facultative anaerobes such as Enterobacteriaceae and Lactobacillaceae can colonize the intestinal lumen due to the higher oxygen content.

Genus and species level

Unclassified species from the genus *Enterococcus (*40.18) was the most common species found in sample 1, and it was similar to a study done by Zwittink RD *et al.,* 2020 and Lee JK *et al.,* 2020.[18,19]

According to Lee JK *et al. 2020*, preterm infants had higher *Enterobacter, Enterococcus, Lactobacillus, Staphylococcus* levels and lower *Bacteroides* and *Bifidobacterium* levels than term neonates [19].

The gut microbiota composition revealed that *Escherichia, Enterobacter, Enterococcus* and *Klebsiella* were more prevalent in preterm infants, according to a study conducted by Van *et al.,* 2020.[20]

Unclassified species from genus *Streptococcus* (32.66) were the most common species in sample 2. It was in concordance with a study conducted by Rutayisire E *et al.,* 2016. They found that babies delivered by caesarean section exhibited less microbial diversity, reduced colonization with *Bacteroides*, *Bifidobacteria*, and *Lactobacilli*, and were likely to have higher *Streptococcus* and *Staphylococcus.*[21]

*In our finding, an unclassified member of the Enterobacteriaceae family (*15.17%*) was the predominant species found in sample 3.* It concorded with a study conducted by Sanidad KZ *et al.,* 2020 who stated that some bacteria, most frequently the gut opportunistic pathobiont E. coli, were discovered in newborns with late-onset sepsis[17].

According to Cuna *et al.,* 2021 and Yoo JY *et al.,* 2020 in disease conditions, there are decreasing commensal obligate anaerobic organisms (e.g., *Bifidobacterium* and *Bacteroides*)and a tendency to be colonized by disease-causing facultative anaerobes (e.g., *Escherichia, Enterobacter* and *Klebsiella*). It was in concordance with our study findings.[10,22]

Correlation with blood culture report

In our study, gut microbiome's dominant bacterial genera matched those isolated from a blood culture. The organism detected by conventional blood culture was the most common OTUs in the gut microbial flora. It concurred with a study done by Stewart *et al., 2017*and Graspeuntner S *et al.,* 2019.[9,23]

Limitation of the study

Due to financial constraints, only three samples were subjected to gut microbiome sequencing. However, this study provides preliminary insights into the gut microbiome composition in neonatal sepsis, highlighting the need for larger, multi-center studies to confirm these associations.

5. CONCLUSION

Gut microbiome analysis revealed that the presence and abundance of *Bifidobacteria* act as a Biomarker for Health. The integrity of the intestinal barrier may be compromised by aberrant gut microbiota in infected neonates, resulting in bacterial translocation into the bloodstream. The presence of *Bifidobacteria* may operate as a signal for protection against gut epithelial translocation. Low *Bifidobacterium* and high facultative anaerobe abundance have been linked to neonatal sepsis. Preterm newborns have a higher risk of sepsis and gut bacterial translocation due to intestinal prematurity, including changes to the gut flora. The leading bacterial genera in the gut microbiome correlate to those recovered in diagnostic blood cultures. Bacteria that cause newborn sepsis frequently live in the infant's intestines before entering the bloodstream. Sepsis may be due to a gut-derived bacterial translocation phenomenon and requires novel strategies for prevention.

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