Gut Microbial Variation May Predict Neonatal Jaundice and Microbial Alterations After Treatment

Juan Ding  
Zhengzhou University First Affiliated Hospital

Xiao Ma  
Zhengzhou University First Affiliated Hospital

Liping Han  
Zhengzhou University First Affiliated Hospital

Xianlan Zhao  
Zhengzhou University First Affiliated Hospital

Ang Li  
Zhengzhou University First Affiliated Hospital

Qi Xin  
Zhengzhou University First Affiliated Hospital

Weining Lian  
Zhengzhou University First Affiliated Hospital

Zhen Li  
Zhengzhou University First Affiliated Hospital

Hongyan Ren  
Zhengzhou University First Affiliated Hospital

Zhigang Ren (fccrenzg@zzu.edu.cn)  
Zhengzhou University First Affiliated Hospital  
https://orcid.org/0000-0003-0798-3444

Research

Keywords: Gut microbiota, Neonatal jaundice, Treatment, MiSeq sequencing

DOI: https://doi.org/10.21203/rs.3.rs-127496/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License
Abstract

**Background:** Neonatal jaundice is a common disease that affects up to 60% of newborns and the relationship between early gut microbiome and development of neonatal jaundice is not fully understood. This study aims to characterize gut microbiome of newborns and to explore its association with risk of neonatal jaundice.

**Methods:** We collected 257 fecal samples from 58 infants at 5 time points of 0, 1, 3, 6 and 12 months prospectively, and finally 114 samples from 6 neonatal jaundice infants (NJI) with treatment and 19 matched non-NJI completed Miseq sequencing and analysis. We characterized gut microbiome, identified microbial differences and gene functions.

**Results:** Meconium microbial diversity from NJI was decreased versus non-NJI. Genus *Gemella* was decreased in NJI versus non-NJI. Eleven predicted microbial functions including fructose-1,6-bisphosphatase III and Pyruvate carboxylase subunit B decreased, while 3 functions including acetyl CoA acyltransferase increased in NJI. After treatments, microbial community presented a significant alterations based beta-diversity. Phylum *Firmicutes* and *Actinobacteria* were increased, while *Proteobacteria* and *Fusobacteria* were decreased. Microbial alterations were also analyzed between 6 recovery NJI and 19 non-NJI.

**Conclusion:** Gut microbiota was unique in meconium microbiome from NJI, implying early gut microbiome intervention could be promising for the management of neonatal jaundice. Alterations of gut microbiota from NJI can be of great value to bolster evidence-based prevention against ‘bacterial dysbiosis’.

**Background**

Neonatal jaundice is the most common condition after birth, and often occurs during the first week of life. About 60% of term infant and 80% of preterm infant develop jaundice in the first week of life[1]. Neonatal jaundice is characterized by the presence of high total serum bilirubin levels and Most cases of neonatal jaundice are considered physiologic[2]. There are studies on the association between physiologic jaundice and adverse long-term health outcomes, such as childhood asthma, type 1 diabetes, and impaired visual function[3–5]. It is essential to understand the relationship between gut microbiome and neonatal jaundice,and to search for new techniques to control the incidence. Recent progress in understanding of microbiota reveals the role of bacteria in bilirubin metabolism. The study in mouse models of germ-free multidrug resistance 2 knockout showed increase serum bilirubin levels[6]. There are study on the possible association between increase in direct bilirubin and bacteria, such as *Bifidobacterium*.[7, 8] Thus, it is hypothesized that gut microbiota is associated with neonatal jaundice but gut microbial characteristics in neonatal jaundice remains limited.

In China, yinzhihuang oral liquid combined with Medilac-Vita (YCM) is often prescribed to infant to treat the neonatal jaundice. However, the infant gut microbiome composition changes on this level is rarely
considered. The infant gut microbiota taxonomic composition and the structure is very different during the first 2–3 years of life.[9] The infant gut microbiota shaped by various factors[10]. One of the most common factors during this period, YCM treatment, can lead to dysbiosis of the infant gut microbiota in early life.

In this study, a total of 58 infants were enrolled, fecal samples separately collected at 0 month (meconium) and 1, 3, 6 and 12 months postpartum. After confirmation, 2 premature infant, 5 infants with incomplete information, 8 NJI with other removing jaundice therapy and 7 infants with antibiotics therapy were excluded. After DNA extraction, 16S rRNA gene sequencing and data quality control, 11 NJI meconium with no sufficient quantity were further discarded. Finally, 6 NJI with YCM treatment and 19 matched non-NJI were included for the final analysis.

We illuminate the association between early neonatal gut microbiome and subsequent diagnosis of neonatal jaundice. Furthermore, we assessed the effect of YCM in the development of infant gut microbiota, and reported when the differences in the gut microbiota of NJI with medication versus non-NJI begin to restoration. The study of the infant gut microbiota development in the context of YCM treatment can be of great value to bolster evidence-based prevention against ‘bacterial dysbiosis’, especially in such a populous territory like China.

**Materials And Methods**

**Participants information**

The study complied with the ethical guidelines of Helsinki Declaration and Rules of Good Clinical Practice. The Institutional Review Board of the First Affiliated Hospital of Zhengzhou University approved the studies 2017-KY-12. Informed consent from all participants was obtained before data and stool samples were collected. Mode of delivery and infants medication use were obtained from hospital electronic medical records. Mothers were asked to complete a questionnaire at each time fecal samples were collected including infant diet (exclusive, partial or no breastfeeding), height and weight of infant and drug use.

**Sample collection and DNA extraction**

The study population was recruited before mothers gave birth. The fecal samples were collected for the first time before infants were exhibiting jaundice and collected in hospital. The others fresh fecal samples were collected at their homes and samples were immediately delivered to the laboratory in dry ice using foam containers. In the laboratory, the sample stored at −80 °C until DNA was extracted. The sample that stayed in room temperature more than 2 hours was discarded. DNA was extracted from fecal samples according to the manufacturer's instructions of E.Z.N.A.® Stool DNA Kit (Omega Bio-tek, Inc., GA). DNA concentration was determined by NanoDrop (Thermo Scientific), and its molecular size was estimated using agarose gel electrophoresis.

**PCR amplification and MiSeq sequencing**
The extracted DNA used as the template to amplify the V3 to V4 regions of 16S rRNA gene. The forward primer (341F) was 5’-CCTACGGGNGGCWGCAG-3’ and the reverse primer (805R) was 5’-GACTACHVGGGTATCTAATCC-3’. The PCR amplification was performed in a EasyCycler 96 PCR system (Analytik Jena Corp., AG) using the following program: 1 cycle of 95 °C for 3 min; 21 cycles of (94°C 30 s; 58°C 30 s; 72°C 30 s); 1 cycle of 72°C 5 min. The products from different samples were indexed and mixed at equal ratios for sequencing according to the manufacturer’s instructions, and the sequencing was performed on the Illumina MiSeq platform at the Shanghai Mobio Biomedical Technology Co. Ltd. Raw Illumina read data for all samples were deposited in the European Bioinformatics Institute European Nucleotide Archive database under accession number PRJNA680178 and PRJNA665920.

**Operational Taxonomic Units (OTUs) and taxonomy annotation**

Equal numbers of reads were randomly chosen from all samples, and then OTUs were binned using UPARSE pipeline[11]. Sequences with 97% similarity level were clustered into OTUs. The software RDP classifier version 2.6[12] was used to assign sequences to the new bacterial taxonomy.

**Bacterial diversity and taxonomic analysis**

Bacterial diversity was assessed by sampling-based analysis of OTUs and presented by ACE index, which was calculated using R program package “vegan”. Principal coordinates analysis (PCoA) and non-metric multidimensional scaling (NMDS) based on OTU abundance and distribution was conducted by R package (http://www. R-project. org/) to analyze microbial communities[13]. The weighted and unweighted Unifrac distances were calculated with phyloseq package[14]. A heatmap of the identified key variables was generated by the Heatmap Builder.

Bacterial differences were compared at the phylum and genus levels. Fecal microbial characteristics were analyzed by linear discriminant analysis (LDA) effect size (LEfSe) method (http://huttenhower.sph.harvard.edu/lefse/)[15]. Using a normalized relative abundance matrix, LEfSe performs the Kruskal-Wallis rank sum test to determine characteristics with significantly different abundances between assigned bacterial and uses LDA to assess the effect size of each characteristics.

**Functional annotation of gut microbial 16S rRNA gene**

To predict the functional profiles of microbial communities based on 16S rRNA gene sequences, we utilized phylogenetic investigation of communities by reconstruction of unobserved states (PICRUSt) version 1.0.0 pipeline[16] and human version 0.99[17] to establish KEGG orthologie (KO) and KEGG pathway/module profile.

**Statistical analysis**

The Wilcoxon rank sum test was used to compare continuous variables between both groups. Fisher’s exact test was used to compare categorical variables. The infant weight-for-length z score were
calculated according to World Health Organization standards[18]. The analyses were performed using SPSS version 21.0. The statistical significance was set at $P < 0.05$.

**Results**

**Characteristics of the participants**

A total of 58 infants (257 fecal samples) from Central China were collected. After a strict pathological diagnosis and exclusion process, 6 NJI with YCM treatment and 19 matched non- NJI were included, a total of 114 fecal samples (Fig. 1). In the meconium cohort, all individuals included were required to the result of full-term, vaginal delivery and exclusive breastfeeding infants. We characterized meconium microbiome among 6 NJI matched 6 non-NJI and identified microbial differences.

Demographic, clinical, and anthropometric characteristics of the 25 neonates are presented in Table 1. Among all participants, there were no significant differences in age, gender, birth weight and birth length between NJI and non-NJI.
Table 1
Characteristics of the study population

| Variables                        | Cases (n = 6)       | Controls (n = 19) | P-value |
|----------------------------------|---------------------|-------------------|---------|
| Maternal age (year)              | 29.67 ± 3.01        | 32.26 ± 4.32      | 0.19    |
| Prenatal BMI (kg/m²)             | 25.72 ± 3.73        | 28.68 ± 3.55      | 0.09    |
| Pregnancy weight gain (kg)       | 13.78 ± 4.52        | 15.88 ± 3.17      | 0.21    |
| Newborn gender                   |                     |                   |         |
| Male                             | 4 (0.67)            | 12 (0.63)         | 0.64    |
| Female                           | 2 (0.33)            | 7 (0.37)          |         |
| Birth weight (g)                 | 3241.67 ± 363.89    | 3489.47 ± 233.68  | 0.06    |
| Birth length (cm)                | 51.67 ± 1.03        | 51.53 ± 1.22      | 0.80    |
| Delivery mode                    |                     |                   |         |
| Vaginal delivery                 | 5 (0.83)            | 12 (0.63)         | 0.35    |
| Caesarean section delivery       | 1 (0.17)            | 7 (0.37)          |         |
| Feeding patterns                 |                     |                   |         |
| Exclusive breastfeeding          | 4 (0.67)            | 15 (0.79)         | 1.00    |
| Non-exclusive breastfeeding      | 2 (0.33)            | 4 (0.21)          |         |
| Apgar score                      | 1 min 9.33 ± 0.82   | 9.37 ± 0.76       | 0.92    |
| 5 min                            | 9.50 ± 0.55         | 9.63 ± 0.50       | 0.59    |
| Gestational age (day)            | 282.17 ± 6.65       | 280.11 ± 8.03     | 0.58    |

Continuous variables was compared using Wilcoxon rank sum test. Fisher’s exact test compared categorical variables.

Gut microbiomes alterations in NJI at 0 month

We collected meconium from NJI and matched non-NJI at 0 month. Compared with the non-NJI, fecal microbial diversity, as estimated by ACE estimator, was markedly decreased in NJI ($P < 0.05$, Fig. 2a, Supplementary Table S1). Moreover, a Venn diagram displaying the overlaps showed that 201 of the total 330 OTUs were shared between NJI and non-NJI (Fig. 2b). Notably, 52 of 253 OTUs were unique for NJI.
To assess similarity among microbial communities, we performed PCoA and NMDS analysis based on unweighted UniFrac distance (Fig. 2c&d, Supplementary Table S2&3).

A heatmap of the identified key variables were revealed and demonstrated that a total of 27 key OTUs were significantly different between NJI and non-NJI (Supplementary Fig. 1, Supplementary Table S4). We further analyzed infant gut microbiota composition and alterations at the phylum and genus levels between two groups. Fecal bacterial composition in each sample at the phylum and genus levels were shown in Supplementary Fig. 2a&b (Supplementary Table S5&S6). Average composition of microbial community at the phylum and genus levels between two groups were shown in Fig. 2e&f, respectively (Supplementary Table S7&S8). Bacterial phyla of Proteobacteria, Firmicutes and Bacteroidetes together accounting for up to 90% of sequences on average, were three dominant populations in two groups (Fig. 2e). Bacterial genera of Escherichia-Shigella, Parabacteroides, Klebsiella and Clostridium_sensu_stricto_1, together accounting for up to 70% of sequences on average, were the four dominant populations in two groups (Fig. 2f). Average amount of Gemella was remarkably decreased in NJI versus non-NJI ($P < 0.05$, Fig. 2g, Supplementary Table S9). Although there were no significant differences in the overall relative abundances of Klebsiella and Clostridium between NJI and non-NJI (both $P > 0.05$ Supplementary Table S9), change of Klebsiella and Clostridium at genus level average were still characterized in NJI (Figs. 2f).

We used the linear discriminant analysis (LDA) Effective Size (LEfSe) to determine the specific bacterial taxa related to neonatal jaundice. A cladogram representative of fecal microbial structure and their predominant bacteria displayed the greatest differences in taxa between NJI and non-NJI (all $P < 0.05$, Supplementary Fig. 3, Supplementary Table S10). Meanwhile, the cladogram of fecal microbial structure between NJI and non-NJI also showed the greatest differences in taxa (all $P < 0.05$, LDA > 2, Fig. 3a, Supplementary Table S10), which suggested gut microbial alterations in NJI.

Microbial metabolic functioning predictions using PICRUSt pipeline[16] to assess the potential microbial functions associated with neonatal jaundice and again showing significant differences between the two groups. Based on LDA selection, 3 predicted microbial functions mainly including acetyl CoA acyltransferase and f 3 oxoacyl acyl carrier protein synthase I enriched, while 11 functions mainly including fructose 1 6 bisphosphatase III, signal peptidase I and YidCOxa1 family membrane protein insertase reduced in NJI versus non NJI (all $P < 0.05$, LDA > 2, Fig. 3b, Supplementary Table S11).

**Gut microbiota temporary dysbiosis between pre-treatment and post-treatment**

The Venn diagram showed overlaps between pre-treatment (0 month) and post-treatment (1 month), revealing that 113 of 214 OTUs were shared between two groups (Fig. 4a). To display microbiome space between pre-treatment and post-treatment, we performed PCoA and NMDS analysis based on unweighted UniFrac distance ($P < 0.05$, Fig. 4b&c, Supplementary Table S12&13). Moreover, PCoA was conducted based on weighted UniFrac distances to assess microbial distribution among 0, 1, 3, 6 and 12 months (Fig. 4d, Supplementary Table S14). PCoA analysis indicated samples tended to be uniform at 0 and 12
month, no obvious separation was observed in YCM treatment. Notably, samples are most heterogeneous at age 1–6 months.

A heatmap of the identified key variables were revealed and demonstrated that a total of 26 key OTUs were significantly different between two groups (Supplementary Fig. 4, Supplementary Table S15). Fecal bacterial composition and difference at the phylum and genus levels between two groups were shown in Fig. 4e&f&g&h, respectively (all $P<0.05$, Supplementary Table S16-19).

We detected the greatest differences in taxa between pre-treatment and post-treatment using the LEfSe method and LDA scores, as shown in Fig. 5a and Supplementary Fig. 5a (all $P<0.05$, LDA > 2.4, Supplementary Table S20).

The predominant fecal microbial functions between pre-treatment and post-treatment were shown by a cladogram and LDA analysis (all $P<0.05$, LDA > 2, Fig. 5b and Supplementary Fig. 5b, Supplementary Table S21). These data revealed significant differences between both groups.

**Gut microbiota alterations in recovery NJI and non-NJI**

The Venn diagram displaying the overlaps showed that 139 of 248 OTUs were shared between recovery NJI and non-NJI at 1 month (Fig. 6a). To display microbiome space between recovery NJI and non-NJI among 0, 1, 3, 6 and 12 months, we performed PCoA analysis based on weighted UniFrac distance (Fig. 6b, Supplementary Table S22). This data revealed that distinct separation bacterial communities were present between recovery NJI and non-NJI at early age, while the microbial communities became more uniform over time.

A heatmap of the identified key variables were revealed and demonstrated that a total of 13 key OTUs were significantly different between recovery NJI and non-NJI at 1 month (Supplementary Fig. 6, Supplementary Table S23). Fecal bacterial composition and difference at the phylum and genus levels between two groups at 1 month were shown in Fig. 6c&d&e&f, respectively (all $P<0.05$, Supplementary Table S24-27).

We detected the greatest differences in taxa between recovery NJI and non-NJI at 1 month using the LEfSe method and LDA scores, as shown in Fig. 7a and Supplementary Fig. 7a (all $P<0.05$, LDA > 3, Supplementary Table S28).

The predominant fecal microbial functions between recovery NJI and non-NJI at 1 month were shown by a cladogram and LDA analysis (all $P<0.05$, LDA > 2, Fig. 7b and Supplementary Fig. 7b, Supplementary Table S29).

**Effect of medication on infant growth**

These observations prompted us to explore the potential relationship between YCM treatment and infant growth. Thus, we examined whether weight-for-length z score at 12 month differed between recovery NJI and non-NJI. Using t-test for independent samples compare the development and growth of recovery NJI
and non-NJI at the 12-Month-old. The infant weight-for-length z score were calculated according to World Health Organization standards. Infant weight-for-length z score at 12 month did not differ significantly between recovery NJI and non-NJI ($P < 0.05$). Our study demonstrates that YCM treatment in early life is independent of growth at the 12 month of age.

**Discussion**

We illustrated that neonatal jaundice was associated with altered composition and function of gut microbiota, as well as decrease of $\alpha$-diversity. Recent studies have reported that higher level of $\alpha$-diversity was associated with lower risk of necrotizing enterocolitis, atopic eczema, and neonatal sepsis[19–21]. Our study suggested that altered microbial community might play an important role during neonatal jaundice initiation and development and higher $\alpha$-diversity of gut microbiome could also be a protective factor for infants at risk of jaundice. Moreover, the bacterial community of neonate at risk of jaundice was separated from that of non-neonatal jaundice.

The gut microbiota is indispensable to the health of the host, healthy infants individuals may share some key microbiota structural features, whereas neonate at risk of jaundice may have aberrant patterns and lack some key bacteria, leading to a ‘dysbiosis’ state. LEfSe analyzed in neonatal jaundice risk present a decrease of some probiotics and butyrate-producing bacteria. Butyrate plays an important role in bacterial energy metabolism and intestinal mucosa health in humans, as the major energy source of the intestinal mucosa, and as an important regulator of gene expression, inflammation, differentiation and apoptosis in host cells[22–25]. It is noteworthy that short chain fatty acids (SCFAs) (particularly propionate and butyrate) initiate within the intestinal mucosa several complementary mechanisms issuing in the activation of intestinal gluconeogenesis[26]. LEfSe shown that some butyrate-producing bacteria, such as *Blautia* and *Pseudobutyrivibrio* were increased in non-NJI versus NJI. Moreover, members of the genus *Blautia* produce acetate, ethanol, hydrogen, lactate, or succinate that can provide the energy for the host[27]. A study indicated that *Pseudobutyrivibrio*, a butyrate, lactic acid and formic acid producer[28]. In addition, members of the genus *Blautia* produce acetate, ethanol, hydrogen, lactate, or succinate that can provide the energy for the host. Moreover, non-NJI harbor more beneficial populations such as *Lachnospiraceae*, one of the major taxonomic groups of the gut microbiota, which degrade complex polysaccharides to SCFAs, including acetate, butyrate, and propionate, which can be used by the host as energy[29]. These results indicated the gut microbial community alteration might play an key role during neonatal jaundice initiation.

Different microbial functions and metabolites are determined by different microbial communities, thereby contributing to the pathogenesis and development of different diseases[7, 30, 31]. Gut microbial functions involved in fructose-1,6-bisphosphatase III and Pyruvate carboxylase subunit B enriched in non-NJI according to the LDA scores (log10). Fructose-1,6-bisphosphatase III, a key enzyme in IGN, exerts important physiological functions in the regulation of energy metabolism and glucose homeostasis[32–34]. Previous studies have shown that increase of lactate was found in cholestasis and are consistent with our results[35, 36]. Lactate is a substrate of intestinal gluconeogenesis. Low levels of expression of
fructose-1,6-bisphosphatase III and Pyruvate carboxylase subunit B enzymes involved in gluconeogenesis decreased clearance of lactate. In addition, in infancy, the body has a great demand for energy and the body may produce more ATP through the glycolysis to maintain energy metabolism, resulting in increased lactate. Thus, the neonate with limited capacity to metabolism of lactate via the intestinal gluconeogenesis may be associated with neonatal jaundice.

Our study analyzed the effect of YCM treatment on gut microbiota of NJI at 0,1,3,6 and 12 months. We found that gut microbiota difference within the YCM treatment group were completely decreased over time, suggesting that YCM treatment can only temporarily perturbation of NJI gut microbiota. Moreover, we conducted a longitudinal study of recovery NJI and non-NJI, PCoA revealed that the microbial community of recovery NJI was clustered with that of non-NJI over time, suggesting microbiota of recovery NJI tends to be recover to similar with non-NJI gradually, and effect of YCM treatment on gut microbiota is temporary. Importantly, infants growth and development at 12 month did not differ significantly between recovery NJI and non-NJI. Taken together, these results demonstrated that gut microbiota composition were influenced by YCM treatment at early, these differences were absent over time and the gut microbiota gradually recovers. Thus, we propose that YCM treatment may have little long term effect on infant healthy.

Conclusions

This study comprehensively characterized gut microbiome in NJI and demonstrated the association between early meconium microbiome and subsequent diagnosis of neonatal jaundice. The combination of early gut microbiome intervention and currently used treatment methods may further benefit NJI. Moreover, we illustrated gut microbial alterations and development in NJI with treatment, which may provide a solid foundation for future health outcomes through microbiota intervention.

List Of Abbreviations

NJI, neonatal jaundice infants; YCM, yinzhihuang oral liquid combined with Medilac-Vita; PCoA, Principal Coordinates Analysis; NMDS, non-metric multidimensional scaling; OTUs, Operational Taxonomy Units; LEfSe, Linear Discriminant Analysis Effect Size; PICRUSt, Phylogenetic Investigation of Communities by Reconstruction of Unobserved States; KO, KEGG orthologue.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the First Affiliated Hospital of Zhengzhou University (2017-XY-012). The study complied with the ethical guidelines of Helsinki Declaration and Rules of Good Clinical Practice. All participants signed written informed consents after the study protocol was fully explained.
Consent for publication

Informed consent from all participants was obtained before data and fecal samples were collected.

Availability of data and materials

The raw Illumina read data for all samples were deposited in the European Bioinformatics Institute European Nucleotide Archive database under the accession number PRJNA680178 and PRJNA6659201.

Competing interests

All authors declare that they have no competing interests.

Funding

This study was sponsored by grants from the National Key Research and Development Program of China (2018YFC20000500), Henan Provincial Medical Science and Technology Project (SBGJ2018004), Henan Province Science and Technology Project (182102310404 and 202102310055), Key Scientific Research Projects of Higher Education Institutions in Henan Province (21A320055 and 20A320056) and National S&T Major Project of China (2018ZX10301201-008). The funding sources had no role in the design of this study nor any role during its execution, analyses, data interpretation, or decision to submit results.

Author contributions

Prof JD and Ms XM conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Ms WL and QX, and Dr LH, XZ, AL, ZL and HR designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. Dr ZR conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Acknowledgements

We thank clinical doctors from the First Affiliated Hospital of Zhengzhou University.

We also thank the generous volunteer subjects who enrolled in the study.

References

1. Rennie J, Burman-Roy S and Murphy MS. Neonatal jaundice: summary of NICE guidance. BMJ (Clinical research ed.) 2010;340:c2409.

2. Dennery PA, Seidman DS and Stevenson DK. Neonatal hyperbilirubinemia. The New England journal of medicine 2001;344:581-90.
3. Huang L, Bao Y, Xu Z, Lei X, Chen Y, Zhang Y, et al. Neonatal bilirubin levels and childhood asthma in the US Collaborative Perinatal Project, 1959-1965. American journal of epidemiology 2013;178:1691-7.

4. McNamee MB, Cardwell CR and Patterson CC. Neonatal jaundice is associated with a small increase in the risk of childhood type 1 diabetes: a meta-analysis of observational studies. Acta diabetologica 2012;49:83-7.

5. Hou C, Norcia AM, Madan A and Good WV. Visuocortical function in infants with a history of neonatal jaundice. Investigative ophthalmology & visual science 2014;55:6443-9.

6. Tabibian JH, O’Hara SP, Trussoni CE, Tietz PS, Splinter PL, Mounajjed T, et al. Absence of the intestinal microbiota exacerbates hepatobiliary disease in a murine model of primary sclerosing cholangitis. Hepatology (Baltimore, Md.) 2016;63:185-96.

7. Zhou S, Wang Z, He F, Qiu H, Wang Y, Wang H, et al. Association of serum bilirubin in newborns affected by jaundice with gut microbiota dysbiosis. The Journal of nutritional biochemistry 2019;63:54-61.

8. Tuzun F, Kumral A, Duman N and Ozkan H. Breast milk jaundice: effect of bacteria present in breast milk and infant feces. Journal of pediatric gastroenterology and nutrition 2013;56:328-32.

9. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, et al. Human gut microbiome viewed across age and geography. Nature 2012;486:222-7.

10. Tamburini S, Shen N, Wu HC and Clemente JC. The microbiome in early life: implications for health outcomes. Nature medicine 2016;22:713-22.

11. Edgar RC. UPARSE: highly accurate OTU sequences from microbial amplicon reads. Nature methods 2013;10:996-8.

12. Wang Q, Garrity GM, Tiedje JM and Cole JR. Naive Bayesian classifier for rapid assignment of rRNA sequences into the new bacterial taxonomy. Applied and environmental microbiology 2007;73:5261-7.

13. Paradis E, Claude J and Strimmer K. APE: Analyses of Phylogenetics and Evolution in R language. Bioinformatics (Oxford, England) 2004;20:289-90.

14. McMurdie PJ and Holmes S. phyloseq: an R package for reproducible interactive analysis and graphics of microbiome census data. PloS one 2013;8:e61217.

15. Segata N, Izard J, Waldron L, Gevers D, Miropolsky L, Garrett WS, et al. Metagenomic biomarker discovery and explanation. Genome biology 2011;12:R60.

16. Langille MG, Zaneveld J, Caporaso JG, McDonald D, Knights D, Reyes JA, et al. Predictive functional profiling of microbial communities using 16S rRNA marker gene sequences. Nature biotechnology 2013;31:814-21.

17. Abubucker S, Segata N, Goll J, Schubert AM, Izard J, Cantarel BL, et al. Metabolic reconstruction for metagenomic data and its application to the human microbiome. PLoS computational biology 2012;8:e1002358.
18. WHO Child Growth Standards based on length/height, weight and age. Acta paediatrica (Oslo, Norway : 1992). Supplement 2006;450:76-85.

19. Warner BB, Deych E, Zhou Y, Hall-Moore C, Weinstock GM, Sodergren E, et al. Gut bacteria dysbiosis and necrotising enterocolitis in very low birthweight infants: a prospective case-control study. Lancet (London, England) 2016;387:1928-36.

20. Abrahamsson TR, Jakobsson HE, Andersson AF, Bjorksten B, Engstrand L and Jenmalm MC. Low diversity of the gut microbiota in infants with atopic eczema. The Journal of allergy and clinical immunology 2012;129:434-40, 40 e1-2.

21. Madan JC, Salari RC, Saxena D, Davidson L, O'Toole GA, Moore JH, et al. Gut microbial colonisation in premature neonates predicts neonatal sepsis. Archives of disease in childhood. Fetal and neonatal edition 2012;97:F456-62.

22. Louis P and Flint HJ. Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine. FEMS microbiology letters 2009;294:1-8.

23. Li F, Hinderberger J, Seedorf H, Zhang J, Buckel W and Thauer RK. Coupled ferredoxin and crotonyl coenzyme A (CoA) reduction with NADH catalyzed by the butyryl-CoA dehydrogenase/Etf complex from Clostridium kluyveri. Journal of bacteriology 2008;190:843-50.

24. Hamer HM, Jonkers D, Venema K, Vanhoutvin S, Troost FJ and Brummer RJ. Review article: the role of butyrate on colonic function. Alimentary pharmacology & therapeutics 2008;27:104-19.

25. Seedorf H, Fricke WF, Veith B, Bruggemann H, Liesegang H, Strittmatter A, et al. The genome of Clostridium kluyveri, a strict anaerobe with unique metabolic features. Proceedings of the National Academy of Sciences of the United States of America 2008;105:2128-33.

26. De Vadder F, Kovatcheva-Datchary P, Goncalves D, Vinera J, Zitoun C, Duchampt A, et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell 2014;156:84-96.

27. Liu C, Finegold SM, Song Y and Lawson PA. Reclassification of Clostridium coccoides, Ruminococcus hansenii, Ruminococcus hydrogenotrophicus, Ruminococcus luti, Ruminococcus productus and Ruminococcus schinkii as Blautia coccoides gen. nov., comb. nov., Blautia hansenii comb. nov., Blautia hydrogenotrophica comb. nov., Blautia luti comb. nov., Blautia producta comb. nov., Blautia schinkii comb. nov. and description of Blautia wexlerae sp. nov., isolated from human faeces. International journal of systematic and evolutionary microbiology 2008;58:1896-902.

28. Paillard D, McKain N, Chaudhary LC, Walker ND, Pizette F, Koppova I, et al. Relation between phylogenetic position, lipid metabolism and butyrate production by different Butyriviribrio-like bacteria from the rumen. Antonie van Leeuwenhoek 2007;91:417-22.

29. Biddle A, Stewart L, Blanchard J and Leschine S. Untangling the Genetic Basis of Fibrolytic Specialization by Lachnospiraceae and Ruminococcaceae in Diverse Gut Communities. Diversity 2013;5:627-40.

30. Sartor RB. Microbial influences in inflammatory bowel diseases. Gastroenterology 2008;134:577-94.

31. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 2011;472:57-63.
32. Benkovic SJ and deMaine MM. Mechanism of action of fructose 1,6-bisphosphatase. Advances in enzymology and related areas of molecular biology 1982;53:45-82.

33. Penhoat A, Fayard L, Stefanutti A, Mithieux G and Rajas F. Intestinal gluconeogenesis is crucial to maintain a physiological fasting glycemia in the absence of hepatic glucose production in mice. Metabolism: clinical and experimental 2014;63:104-11.

34. Soty M, Gautier-Stein A, Rajas F and Mithieux G. Gut-Brain Glucose Signaling in Energy Homeostasis. Cell metabolism 2017;25:1231-42.

35. Long Y, Dong X, Yuan Y, Huang J, Song J, Sun Y, et al. Metabolomics changes in a rat model of obstructive jaundice: mapping to metabolism of amino acids, carbohydrates and lipids as well as oxidative stress. Journal of clinical biochemistry and nutrition 2015;57:50-9.

36. Fabbri C, de Cassia Mascarenhas-Netto R, Lalwani P, Melo GC, Magalhaes BM, Alexandre MA, et al. Lipid peroxidation and antioxidant enzymes activity in Plasmodium vivax malaria patients evolving with cholestatic jaundice. Malaria journal 2013;12:315.

Figures
Study design and flow diagram. A total of 257 fecal samples from 17 NJI and 41 non-NJI were collected. After a strict pathologic diagnosis and exclusion process, the remained samples were used for DNA extraction, 16S rRNA sequencing and data quality control. Finally, 6 NJI with YCM treatment and 19 non-NJI were utilized for bioinformatics analysis. NJI: neonatal jaundice infants; YCM: yinzhihuang oral liquid combined with Medilac-Vita.
Study design and flow diagram. A total of 257 fecal samples from 17 NJI and 41 non-NJI were collected. After a strict pathologic diagnosis and exclusion process, the remained samples were used for DNA extraction, 16S rRNA sequencing and data quality control. Finally, 6 NJI with YCM treatment and 19 non-NJI were utilized for bioinformatics analysis. NJI: neonatal jaundice infants; YCM: yinzhihuang oral liquid combined with Medilac-Vita.
Study design and flow diagram. A total of 257 fecal samples from 17 NJI and 41 non-NJI were collected. After a strict pathologic diagnosis and exclusion process, the remained samples were used for DNA extraction, 16S rRNA sequencing and data quality control. Finally, 6 NJI with YCM treatment and 19 non-NJI were utilized for bioinformatics analysis. NJI: neonatal jaundice infants; YCM: yinzhihuang oral liquid combined with Medilac-Vita.
Study design and ow diagram. A total of 257 fecal samples from 17 NJI and 41 non-NJI were collected. After a strict pathologic diagnosis and exclusion process, the remained samples were used for DNA extraction, 16S rRNA sequencing and data quality control. Finally, 6 NJI with YCM treatment and 19 non-NJI were utilized for bioinformatics analysis. NJI: neonatal jaundice infants; YCM: yinzhihuang oral liquid combined with Medilac-Vita.
Figure 1

Study design and flow diagram. A total of 257 fecal samples from 17 NJI and 41 non-NJI were collected. After a strict pathologic diagnosis and exclusion process, the remained samples were used for DNA extraction, 16S rRNA sequencing and data quality control. Finally, 6 NJI with YCM treatment and 19 non-NJI were utilized for bioinformatics analysis. NJI: neonatal jaundice infants; YCM: yinzhihuang oral liquid combined with Medilac-Vita.
Figure 2

Altered meconium microbiota composition in NJI. (a) Microbial alpha diversity decreased in NJI shown by the ACE estimator. (b) A Venn diagram displaying the overlaps showed that 201 of the total 330 OTUs were shared between NJI and non-NJI. Overall diversity was calculated using unweighted UniFrac by PCoA (c) and NMDS (d), indicating a separation on samples between NJI and non-NJI. Fecal microbiota composition at the phylum level (e) and genus level (f) between NJI and non-NJI. (g) Compared with non-NJI, 1 genus was significantly decreased in NJI (P < 0.05). NJI: neonatal jaundice infants; OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling.
Figure 2

Altered meconium microbiota composition in NJI. (a) Microbial alpha diversity decreased in NJI shown by the ACE estimator. (b) A Venn diagram displaying the overlaps showed that 201 of the total 330 OTUs were shared between NJI and non-NJI. Overall diversity was calculated using unweighted UniFrac by PCoA (c) and NMDS (d), indicating a separation on samples between NJI and non-NJI. Fecal microbiota composition at the phylum level (e) and genus level (f) between NJI and non-NJI. (g) Compared with non-NJI, 1 genus was significantly decreased in NJI (P < 0.05). NJI: neonatal jaundice infants; OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling.
Figure 2

Altered meconium microbiota composition in NJI. (a) Microbial alpha diversity decreased in NJI shown by the ACE estimator. (b) A Venn diagram displaying the overlaps showed that 201 of the total 330 OTUs were shared between NJI and non-NJI. Overall diversity was calculated using unweighted UniFrac by PCoA (c) and NMDS (d), indicating a separation on samples between NJI and non-NJI. Fecal microbiota composition at the phylum level (e) and genus level (f) between NJI and non-NJI. (g) Compared with non-NJI, 1 genus was significantly decreased in NJI (P < 0.05). NJI: neonatal jaundice infants; OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling.
Figure 2

Altered meconium microbiota composition in NJI. (a) Microbial alpha diversity decreased in NJI shown by the ACE estimator. (b) A Venn diagram displaying the overlaps showed that 201 of the total 330 OTUs were shared between NJI and non-NJI. Overall diversity was calculated using unweighted UniFrac by PCoA (c) and NMDS (d), indicating a separation on samples between NJI and non-NJI. Fecal microbiota composition at the phylum level (e) and genus level (f) between NJI and non-NJI. (g) Compared with non-NJI, 1 genus was significantly decreased in NJI (P < 0.05). NJI: neonatal jaundice infants; OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling.
Figure 2

Altered meconium microbiota composition in NJI. (a) Microbial alpha diversity decreased in NJI shown by the ACE estimator. (b) A Venn diagram displaying the overlaps showed that 201 of the total 330 OTUs were shared between NJI and non-NJI. Overall diversity was calculated using unweighted UniFrac by PCoA (c) and NMDS (d), indicating a separation on samples between NJI and non-NJI. Fecal microbiota composition at the phylum level (e) and genus level (f) between NJI and non-NJI. (g) Compared with non-NJI, 1 genus was significantly decreased in NJI (P < 0.05). NJI: neonatal jaundice infants; OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling.
Figure 2

Altered meconium microbiota composition in NJI. (a) Microbial alpha diversity decreased in NJI shown by the ACE estimator. (b) A Venn diagram displaying the overlaps showed that 201 of the total 330 OTUs were shared between NJI and non-NJI. Overall diversity was calculated using unweighted UniFrac by PCoA (c) and NMDS (d), indicating a separation on samples between NJI and non-NJI. Fecal microbiota composition at the phylum level (e) and genus level (f) between NJI and non-NJI. (g) Compared with non-NJI, 1 genus was significantly decreased in NJI (P < 0.05). NJI: neonatal jaundice infants; OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling.
Identification of specific bacterial taxa and microbial functions associated with neonatal jaundice. (a) The greatest differences in taxa between NJI and non-NJI are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between NJI and non-NJI based on the LDA scores (log10). NJI: neonatal jaundice infants; LDA: linear discriminant analysis.
Identification of specific bacterial taxa and microbial functions associated with neonatal jaundice. (a) The greatest differences in taxa between NJI and non-NJI are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between NJI and non-NJI based on the LDA scores (log10). NJI: neonatal jaundice infants; LDA: linear discriminant analysis.
Figure 3

Identification of specific bacterial taxa and microbial functions associated with neonatal jaundice. (a) The greatest differences in taxa between NJI and non-NJI are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between NJI and non-NJI based on the LDA scores (log10). NJI: neonatal jaundice infants; LDA: linear discriminant analysis.
Figure 3

Identification of specific bacterial taxa and microbial functions associated with neonatal jaundice. (a) The greatest differences in taxa between NJI and non-NJI are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between NJI and non-NJI based on the LDA scores (log10). NJI: neonatal jaundice infants; LDA: linear discriminant analysis.
Figure 3

Identification of specific bacterial taxa and microbial functions associated with neonatal jaundice. (a) The greatest differences in taxa between NJI and non-NJI are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between NJI and non-NJI based on the LDA scores (log10). NJI: neonatal jaundice infants; LDA: linear discriminant analysis.
Figure 3

Identification of specific bacterial taxa and microbial functions associated with neonatal jaundice. (a) The greatest differences in taxa between NJI and non-NJI are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between NJI and non-NJI based on the LDA scores (log10). NJI: neonatal jaundice infants; LDA: linear discriminant analysis.
Figure 4

Gut microbial differences of infants between pre-treatment (0 month) and post-treatment (1 month). (a) A Venn diagram displaying the overlaps showed that 113 of 214 OTUs were shared between pre-treatment and post-treatment. Overall diversity was calculated using unweighted UniFrac by PCoA (b) and NMDS (c), indicating a separation on samples between pre-treatment and post-treatment. (d) PCoA based on the weighted UniFrac distance in YCM treatment to assess microbial distribution among 0, 1, 3, 6 and 12 months, indicating that samples tended to be uniform at 0 and 12 month, and samples are most heterogeneous at 1-6 months. Fecal microbiota composition at the phylum level (e) and genus level (f) between pre-treatment and post-treatment. (g) Compared with pre-treatment, 2 phyla were significantly increased, while 2 phyla were significantly decreased in post-treatment (all P < 0.05). (h) One genus was increased, whereas 1 genus was decreased in pre-treatment versus post-treatment (all P < 0.05). OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling; YCM: yinzhihuang oral liquid combined with Medilac-Vita; M0: 0 month; M1: 1 month; M3: 3 months; M6: 6 months; M12: 12 months.
Figure 4

Gut microbial differences of infants between pre-treatment (0 month) and post-treatment (1 month). (a) A Venn diagram displaying the overlaps showed that 113 of 214 OTUs were shared between pre-treatment and post-treatment. Overall diversity was calculated using unweighted UniFrac by PCoA (b) and NMDS (c), indicating a separation on samples between pre-treatment and post-treatment. (d) PCoA based on the weighted UniFrac distance in YCM treatment to assess microbial distribution among 0, 1, 3, 6 and 12 months, indicating that samples tended to be uniform at 0 and 12 month, and samples are most heterogeneous at 1-6 months. Fecal microbiota composition at the phylum level (e) and genus level (f) between pre-treatment and post-treatment. (g) Compared with pre-treatment, 2 phyla were significantly increased, while 2 phyla were significantly decreased in post-treatment (all P < 0.05). (h) One genus was increased, whereas 1 genus was decreased in pre-treatment versus post-treatment (all P < 0.05). OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling; YCM: yinzhihuang oral liquid combined with Medilac-Vita; M0: 0 month; M1: 1 month; M3: 3 months; M6: 6 months; M12: 12 months.
Figure 4

Gut microbial differences of infants between pre-treatment (0 month) and post-treatment (1 month). (a) A Venn diagram displaying the overlaps showed that 113 of 214 OTUs were shared between pre-treatment and post-treatment. Overall diversity was calculated using unweighted UniFrac by PCoA (b) and NMDS (c), indicating a separation on samples between pre-treatment and post-treatment. (d) PCoA based on the weighted UniFrac distance in YCM treatment to assess microbial distribution among 0, 1, 3, 6 and 12 months, indicating that samples tended to be uniform at 0 and 12 month, and samples are most heterogeneous at 1-6 months. Fecal microbiota composition at the phylum level (e) and genus level (f) between pre-treatment and post-treatment. (g) Compared with pre-treatment, 2 phyla were significantly increased, while 2 phyla were significantly decreased in post-treatment (all P < 0.05). (h) One genus was increased, whereas 1 genus was decreased in pre-treatment versus post-treatment (all P < 0.05). OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling; YCM: yinzhihuang oral liquid combined with Medilac-Vita; M0: 0 month; M1: 1 month; M3: 3 months; M6: 6 months; M12: 12 months.
Figure 4

Gut microbial differences of infants between pre-treatment (0 month) and post-treatment (1 month). (a) A Venn diagram displaying the overlaps showed that 113 of 214 OTUs were shared between pre-treatment and post-treatment. Overall diversity was calculated using unweighted UniFrac by PCoA (b) and NMDS (c), indicating a separation on samples between pre-treatment and post-treatment. (d) PCoA based on the weighted UniFrac distance in YCM treatment to assess microbial distribution among 0, 1, 3, 6 and 12 months, indicating that samples tended to be uniform at 0 and 12 month, and samples are most heterogeneous at 1-6 months. Fecal microbiota composition at the phylum level (e) and genus level (f) between pre-treatment and post-treatment. (g) Compared with pre-treatment, 2 phyla were significantly increased, while 2 phyla were significantly decreased in post-treatment (all P < 0.05). (h) One genus was increased, whereas 1 genus was decreased in pre-treatment versus post-treatment (all P < 0.05). OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling; YCM: yinzhihuang oral liquid combined with Medilac-Vita; M0: 0 month; M1: 1 month; M3: 3 months; M6: 6 months; M12: 12 months.
Figure 4

Gut microbial differences of infants between pre-treatment (0 month) and post-treatment (1 month). (a) A Venn diagram displaying the overlaps showed that 113 of 214 OTUs were shared between pre-treatment and post-treatment. Overall diversity was calculated using unweighted UniFrac by PCoA (b) and NMDS (c), indicating a separation on samples between pre-treatment and post-treatment. (d) PCoA based on the weighted UniFrac distance in YCM treatment to assess microbial distribution among 0, 1, 3, 6 and 12 months, indicating that samples tended to be uniform at 0 and 12 month, and samples are most heterogeneous at 1-6 months. Fecal microbiota composition at the phylum level (e) and genus level (f) between pre-treatment and post-treatment. (g) Compared with pre-treatment, 2 phyla were significantly increased, while 2 phyla were significantly decreased in post-treatment (all P < 0.05). (h) One genus was increased, whereas 1 genus was decreased in pre-treatment versus post-treatment (all P < 0.05). OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling; YCM: yinzhihuang oral liquid combined with Medilac-Vita; M0: 0 month; M1: 1 month; M3: 3 months; M6: 6 months; M12: 12 months.
Gut microbial differences of infants between pre-treatment (0 month) and post-treatment (1 month). (a) A Venn diagram displaying the overlaps showed that 113 of 214 OTUs were shared between pre-treatment and post-treatment. Overall diversity was calculated using unweighted UniFrac by PCoA (b) and NMDS (c), indicating a separation on samples between pre-treatment and post-treatment. (d) PCoA based on the weighted UniFrac distance in YCM treatment to assess microbial distribution among 0, 1, 3, 6 and 12 months, indicating that samples tended to be uniform at 0 and 12 month, and samples are most heterogeneous at 1-6 months. Fecal microbiota composition at the phylum level (e) and genus level (f) between pre-treatment and post-treatment. (g) Compared with pre-treatment, 2 phyla were significantly increased, while 2 phyla were significantly decreased in post-treatment (all P < 0.05). (h) One genus was increased, whereas 1 genus was decreased in pre-treatment versus post-treatment (all P < 0.05). OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling; YCM: yinzhihuang oral liquid combined with Medilac-Vita; M0: 0 month; M1: 1 month; M3: 3 months; M6: 6 months; M12: 12 months.
Figure 5

Identification of specific bacterial taxa and microbial functions between pre-treatment (0 month) and post-treatment (1 month). (a) The greatest differences in taxa between pre-treatment and post-treatment are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between pre-treatment and post-treatment based on the LDA scores (log10). LDA: linear discriminant analysis; M0: 0 month; M1: 1 month.
Figure 5

Identification of specific bacterial taxa and microbial functions between pre-treatment (0 month) and post-treatment (1 month). (a) The greatest differences in taxa between pre-treatment and post-treatment are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between pre-treatment and post-treatment based on the LDA scores (log10). LDA: linear discriminant analysis; M0: 0 month; M1: 1 month.
Figure 5

Identification of specific bacterial taxa and microbial functions between pre-treatment (0 month) and post-treatment (1 month). (a) The greatest differences in taxa between pre-treatment and post-treatment are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between pre-treatment and post-treatment based on the LDA scores (log10). LDA: linear discriminant analysis; M0: 0 month; M1: 1 month.
Figure 5

Identification of specific bacterial taxa and microbial functions between pre-treatment (0 month) and post-treatment (1 month). (a) The greatest differences in taxa between pre-treatment and post-treatment are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between pre-treatment and post-treatment based on the LDA scores (log10). LDA: linear discriminant analysis; M0: 0 month; M1: 1 month.
Figure 5

Identification of specific bacterial taxa and microbial functions between pre-treatment (0 month) and post-treatment (1 month). (a) The greatest differences in taxa between pre-treatment and post-treatment are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between pre-treatment and post-treatment based on the LDA scores (log10). LDA: linear discriminant analysis; M0: 0 month; M1: 1 month.
Identification of specific bacterial taxa and microbial functions between pre-treatment (0 month) and post-treatment (1 month). (a) The greatest differences in taxa between pre-treatment and post-treatment are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between pre-treatment and post-treatment based on the LDA scores (log10). LDA: linear discriminant analysis; M0: 0 month; M1: 1 month.
Figure 6

Gut microbial alterations of infants between recovery NJI and non-NJI. (a) A Venn diagram displaying the overlaps showed that 139 of 248 OTUs were shared between recovery NJI and non-NJI. (b) PCoA based on the weighted UniFrac distance between recovery NJI and non-NJI among 0, 1, 3, 6 and 12 months, indicating that the microbial communities became more uniform over time. Fecal microbiota composition at the phylum level (c) and genus level (d) between recovery NJI and non-NJI. (e) Compared with recovery NJI, 1 phylum was significantly decreased in non-NJI (P < 0.05). (f) Three genera were increased in non-NJI versus recovery NJI(all P < 0.05). NJI: neonatal jaundice infants; OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling; M0: 0 month; M1: 1 month; M3: 3 months; M6: 6 months; M12: 12 months.
Figure 6

Gut microbial alterations of infants between recovery NJI and non-NJI. (a) A Venn diagram displaying the overlaps showed that 139 of 248 OTUs were shared between recovery NJI and non-NJI. (b) PCoA based on the weighted UniFrac distance between recovery NJI and non-NJI among 0, 1, 3, 6 and 12 months, indicating that the microbial communities became more uniform over time. Fecal microbiota composition at the phylum level (c) and genus level (d) between recovery NJI and non-NJI. (e) Compared with recovery NJI, 1 phylum was significantly decreased in non-NJI (P < 0.05). (f) Three genera were increased in non-NJI versus recovery NJI (all P < 0.05). NJI: neonatal jaundice infants; OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling; M0: 0 month; M1: 1 month; M3: 3 months; M6: 6 months; M12: 12 months.
Figure 6

Gut microbial alterations of infants between recovery NJI and non-NJI. (a) A Venn diagram displaying the overlaps showed that 139 of 248 OTUs were shared between recovery NJI and non-NJI. (b) PCoA based on the weighted UniFrac distance between recovery NJI and non-NJI among 0, 1, 3, 6 and 12 months, indicating that the microbial communities became more uniform over time. Fecal microbiota composition at the phylum level (c) and genus level (d) between recovery NJI and non-NJI. (e) Compared with recovery NJI, 1 phylum was significantly decreased in non-NJI (P < 0.05). (f) Three genera were increased in non-NJI versus recovery NJI (all P < 0.05). NJI: neonatal jaundice infants; OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling; M0: 0 month; M1: 1 month; M3: 3 months; M6: 6 months; M12: 12 months.
Figure 6

Gut microbial alterations of infants between recovery NJI and non-NJI. (a) A Venn diagram displaying the overlaps showed that 139 of 248 OTUs were shared between recovery NJI and non-NJI. (b) PCoA based on the weighted UniFrac distance between recovery NJI and non-NJI among 0, 1, 3, 6 and 12 months, indicating that the microbial communities became more uniform over time. Fecal microbiota composition at the phylum level (c) and genus level (d) between recovery NJI and non-NJI. (e) Compared with recovery NJI, 1 phylum was significantly decreased in non-NJI (P < 0.05). (f) Three genera were increased in non-NJI versus recovery NJI(all P < 0.05). NJI: neonatal jaundice infants; OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling; M0: 0 month; M1: 1 month; M3: 3 months; M6: 6 months; M12: 12 months.
Figure 6

Gut microbial alterations of infants between recovery NJI and non-NJI. (a) A Venn diagram displaying the overlaps showed that 139 of 248 OTUs were shared between recovery NJI and non-NJI. (b) PCoA based on the weighted UniFrac distance between recovery NJI and non-NJI among 0, 1, 3, 6 and 12 months, indicating that the microbial communities became more uniform over time. Fecal microbiota composition at the phylum level (c) and genus level (d) between recovery NJI and non-NJI. (e) Compared with recovery NJI, 1 phylum was significantly decreased in non-NJI (P < 0.05). (f) Three genera were increased in non-NJI versus recovery NJI (all P < 0.05). NJI: neonatal jaundice infants; OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling; M0: 0 month; M1: 1 month; M3: 3 months; M6: 6 months; M12: 12 months.
Figure 6

Gut microbial alterations of infants between recovery NJI and non-NJI. (a) A Venn diagram displaying the overlaps showed that 139 of 248 OTUs were shared between recovery NJI and non-NJI. (b) PCoA based on the weighted UniFrac distance between recovery NJI and non-NJI among 0, 1, 3, 6 and 12 months, indicating that the microbial communities became more uniform over time. Fecal microbiota composition at the phylum level (c) and genus level (d) between recovery NJI and non-NJI. (e) Compared with recovery NJI, 1 phylum was significantly decreased in non-NJI (P < 0.05). (f) Three genera were increased in non-NJI versus recovery NJI(all P < 0.05). NJI: neonatal jaundice infants; OTUs: Operational Taxonomy Units; PCoA: principal coordinates analysis; NMDS: non-metric multidimensional scaling; M0: 0 month; M1: 1 month; M3: 3 months; M6: 6 months; M12: 12 months.
Figure 7

Identification of specific bacterial taxa and microbial functions between recovery NJI and non-NJI. (a) The greatest differences in taxa between recovery NJI and non-NJI are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between recovery NJI and non-NJI based on the LDA scores (log10). NJI: neonatal jaundice infants; LDA: linear discriminant analysis.
Identification of specific bacterial taxa and microbial functions between between recovery NJI and non-NJI. (a) The greatest differences in taxa between recovery NJI and non-NJI are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between recovery NJI and non-NJI based on the LDA scores (log10). NJI: neonatal jaundice infants; LDA: linear discriminant analysis.

**Figure 7**

Identification of specific bacterial taxa and microbial functions between between recovery NJI and non-NJI. (a) The greatest differences in taxa between recovery NJI and non-NJI are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between recovery NJI and non-NJI based on the LDA scores (log10). NJI: neonatal jaundice infants; LDA: linear discriminant analysis.
Figure 7

Identification of specific bacterial taxa and microbial functions between recovery NJI and non-NJI. (a) The greatest differences in taxa between recovery NJI and non-NJI are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between recovery NJI and non-NJI based on the LDA scores (log10). NJI: neonatal jaundice infants; LDA: linear discriminant analysis.
Identification of specific bacterial taxa and microbial functions between between recovery NJI and non-NJI. (a) The greatest differences in taxa between recovery NJI and non-NJI are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between recovery NJI and non-NJI based on the LDA scores (log10). NJI: neonatal jaundice infants; LDA: linear discriminant analysis.

Figure 7

Identification of specific bacterial taxa and microbial functions between between recovery NJI and non-NJI. (a) The greatest differences in taxa between recovery NJI and non-NJI are presented according to the LDA scores (log10). (b) Differences in gut microbial functions between recovery NJI and non-NJI based on the LDA scores (log10). NJI: neonatal jaundice infants; LDA: linear discriminant analysis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigures.pdf
- SupplementaryFigures.pdf
- SupplementaryFigures.pdf
- SupplementaryFigures.pdf
- SupplementaryFigures.pdf
- SupplementaryTableS10.xls
- SupplementaryTableS10.xls
- SupplementaryTableS1.xls
- SupplementaryTableS10.xls
• SupplementaryTableS22.xls
• SupplementaryTableS19.xls
• SupplementaryTableS22.xls
• SupplementaryTableS16.xls
• SupplementaryTableS22.xls
• SupplementaryTableS23.xls
• SupplementaryTableS23.xls
• SupplementaryTableS24.xls
• SupplementaryTableS23.xls
• SupplementaryTableS22.xls
• SupplementaryTableS23.xls
• SupplementaryTableS25.xls
• SupplementaryTableS25.xls
• SupplementaryTableS25.xls
• SupplementaryTableS25.xls
• SupplementaryTableS25.xls
• SupplementaryTableS19.xls
• SupplementaryTableS24.xls
• SupplementaryTableS26.xls
• SupplementaryTableS26.xls
• SupplementaryTableS27.xls
• SupplementaryTableS27.xls
• SupplementaryTableS27.xls
• SupplementaryTableS24.xls
• SupplementaryTableS28.xls
• SupplementaryTableS28.xls
• SupplementaryTableS28.xls
• SupplementaryTableS26.xls
• SupplementaryTableS23.xls
• SupplementaryTableS25.xls
• SupplementaryTableS25.xls
• SupplementaryTableS28.xls
• SupplementaryTableS28.xls
• SupplementaryTableS20.xls
• SupplementaryTableS3.xls
• SupplementaryTableS27.xls
• SupplementaryTableS21.xls
• SupplementaryTableS4.xls
• SupplementaryTableS29.xls
• SupplementaryTableS22.xls
• SupplementaryTableS5.xls
