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Effect of Antibiotics on The Gut Microbiota in Children with Chronic Pancreatitis

Wei Wang[1#], Yuan Xiao[2#], Shuang Ma[3#], Xinqiong Wang[2], Ting Wang[4], Chundi Xv[2], Yiran Zhou[1*] and Biao Gong[5*]

[1]Department of General Surgery and Research Institute of Pancreatic Diseases, Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200025, China

[2]Pediatric Department, Ruijin Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China

[3]School of life sciences, School of life sciences Fudan University, Shanghai, China

[4]Department of Pathology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, P.R. China

[5]Gastroenterology Department of Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China

[*]Corresponding author:

Yiran Zhou,
Department of General Surgery and Research Institute of Pancreatic Diseases, Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University, 197 Ruijin 2nd road, Shanghai 200025, China,
E-mail: eydzyr@163.com, wangwei_0306@163.com

Biao Gong,
Gastroenterology Department of Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, E-mail: gbercp@163.com

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[#]Author Contributions:

Wei Wang, Yuan Xiao, and Shuang Ma, These authors are contributed to equally this this article

1. Abstract

1.1. Objectives: Little is known about the effect of antibiotic treatment on the gut microbiota in children with chronic pancreatitis (CCP). Our objective was to identify the effect of antibiotic treatment on the gut microbiota in children with chronic pancreatitis (CCP), the main gut microbiota genera and characterize the patients' functional mutations after using antibiotics.

1.2. Methods: The 16S rRNA sequencing method was used to compare the gut microbiota of healthy controls (HCs) with CCP using and not using antibiotics.

1.3. Results: All CCP demonstrated a significantly reduced alpha diversity of the gut microbiota ($P < 0.01$). The gut microbiota's alpha diversity and the abundance of genera's beta diversity did not show statistical differences between the non-antibiotics and antibiotics groups. There were 15 altered genera with common abundance in the non-antibiotics and antibiotics groups compared to the HC group. The area under the curve (AUC) of the top three probiotics, i.e., Faecalibacterium, Eubacterium, and Subdoligranulum, was 0.91. Among the 13 genera altered in the non-antibiotics group, the top three genera were not appropriate as biomarkers for cases receiving antibiotics. Compared to these 13 genera, the differences between the genera and the proportion of gram-positive bacteria in the 17 genera altered only in the antibiotics group were not statistically significant. The Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis indicated that the antibiotics caused alterations in the abundance of certain genera. The enriched functions and the altered gut microbiota in the two groups had their enriched functions.

1.4. Conclusion: The use of antibiotics affects the gut microbiota of CCP, but the effect of disease on gut microbiota is still obvious, which may help diagnosis and further investigation into the pathogenic mechanisms of CP.

Chronic pancreatitis (CP) is a persistent fibro-inflammatory process of the pancreas associated with genetic, environmental, and other pathogenic factors. This disease eventually led to the pancreas' irreversible injury and increased risk of pancreatic cancer and impaired mental health [1-3].

Several evidence has shown that gut microbiota interaction led to the onset and clinical presentation of CP. Participants who received antibiotics or probiotics within 1 month or 3 months before sample collection were excluded [3,4] However, in some instances of an acute episode of CP, patients often present higher leukocyte levels, and some hospitals might opt to treat or prevent the infection with antibiotics, and we did not know the specific antibiotics used before admission [5]. Serial studies have revealed that antibiotics alter the abundance and composition of the gut microbiota. The altering capacity depends on the drug class, pharmacokinetics, pharmacodynamics, range of action, dosage, duration, and administration route, causing an increase in the disease's risk, secondary infections allergy, and obesity and the spread of drug-resistant pathogens [6, 7]. However, only a few studies on the gut microbiota of children with CP (CCP) are undergoing antibiotic use within the previous 3 months before admission.

The effect of antibiotic treatment on the gut microbiota in the CCP and any difference in the previous treatment results and the antibiotic treatment remains unclear. Therefore, we further analyzed the outcomes in the CCP with antibiotic use by employing the 16S rRNA sequencing method, based on the next-generation sequencing method described in our previous study [3].

2. Material and Methods

2.1. Inclusion and exclusion criteria

The diagnosis of CP was based on the International Study Group of Pediatric Pancreatitis criteria, In Search for a Cure (INSPPIRE), as previously described [3,8]. All cases and healthy controls (HCs) were 4 to 18 years old and were examined from 2014 to 2017 [3]. Individuals who used (antibiotics group) and not used (non-antibiotics group) antibiotic(s) or an oral probiotic drink within the previous 3 months were included in the study.

This study was performed in accordance with relevant guidelines and regulations and approved by the Institutional Review Board (IRB) of Shanghai Jiaotong University, and the protocols were approved by the Committee of Human Subjects Protection of the Ruijin Hospital. Informed consent was obtained from the parents of all recruited children. The clinical trial registry number is NCT03809247 [3].

Collection of samples, isolation of fecal bacterial DNA, Illumina MiSeq sequencing, processing of sequencing data, and statistical analysis were consistent with our previous paper [3].

3. Results

3.1. Basic Clinical Data

The antibiotics group included ten patients, as is shown in Table 1. The information of the non-antibiotic group (n=30) and the HCs group (n=35) have been shown in the previous study [3]. Significant differences were not found between the antibiotics and HCs groups in terms of age (8.6 ± 1.1 vs 7.2 ± 0.5 years, P = 0.2181) and sex ratio (50.0% vs 65.7% men, P = 0.366). In addition, significant differences were not found between the antibiotics and non-antibiotics groups in terms of age (8.6 ± 1.1 vs 8.3 ± 0.7 years, P = 0.8086), sex ratio (50.0% vs 46.7% men, P = 0.855), and duration of diseases (13.0 ± 19.0 vs 20.0 ± 25.6 years, P = 0.4318).

Table: 1 Basic clinical data of CCP who have taken antibiotics.

Patient ID	Sex	Age (ys)	Dur (ms)	Clinical Symptoms*	ERCP findings
CCP+A-1	Male	12	0.7	Repeated abdominal pain, nausea, vomiting	Pancreatic duct stricture and dilation
CCP+A-2	Male	12	36	Repeated abdominal pain	Pancreatic duct dilation
CCP+A-3	Female	6	0.7	Repeated abdominal pain	Anomalous junction of pancreaticobiliary duct
CCP+A-4	Female	9	2	Repeated abdominal pain	Pancreatic duct stones, anomalous junction of pancreaticobiliary duct,
CCP+A-5	Male	4	0.2	Abdominal pain	Pancreatic duct dilation
CCP+A-6	Male	13	36	Repeated abdominal pain	Pancreatic duct dilation ,Pancreas divisum
CCP+A-7	Female	9	1	Repeated abdominal pain, nausea, vomiting	/(MRCP: Pancreatic duct stricture)
CCP+A-8	Female	9	48	Repeated abdominal pain	/(MRCP: Pancreatic duct dilation)
CCP+A-9	Male	9	4	Repeated abdominal pain	Pancreatic duct stricture
CCP+A-10	Female	3	1	Repeated abdominal pain	Pancreatic duct stones,

3.2. Alterations of Gut Microbial Diversity in CCP

All CCP demonstrated a significantly reduced alpha diversity of the gut microbiota ($P < 0.01$; Figure 1A). An analysis of the beta diversity revealed that the abundance of genera (non-antibiotics group vs. HCs group; antibiotics group vs. HCs group) had distinct clustering (Figure 1B and C). The gut microbiota's alpha diversity differences did not reveal statistical differences between the non-antibiotics and antibiotics groups (Figure 1A). In addition, the analysis of beta diversity demonstrated that the abundance of genera had no distinct clustering between the non-antibiotics and antibiotics groups (Figure 1B and C).

There were 15 altered genera with common abundance in the non-antibiotics and antibiotics groups compared to the HC group, including nine genera with decreased abundance (Faecalibacterium, Eubacterium, Subdoligranulum, Roseburia, Fusicatenibacter, Lachnospiraceae, Erysipelotrichaceae, Ruminiclostridium, and Parasutterella) (Figure

2A–I) and six genera with increased abundance (Streptococcus, Enterococcus, Lactobacillus, Klebsiella, Actinomyces, and Rhodococcus) (Fig. 2J–O). Most (73.3%; 11/15) of the altered genera belonged to Firmicutes, 13.3% (2/15) to Actinobacteria, and 13.3% (2/15) to Proteobacteria (Supplementary Figure 1A). Most (86.7%) of them were gram-positive strains, and 13.3% were gram-negative strains (Supplementary Figure 1B). The area under receiver operating characteristics (AUROC) curve was used to analyze the top three probiotics whose abundance decreased greatly in CCP treated with antibiotics. The AUC of Faecalibacterium, Subdoligranulum, and Eubacterium was 0.87 (0.76–0.87, P＜0.0001), 0.78 (0.65–0.78, P＜0.01), and 0.81 (0.64–0.78, P＜0.01), respectively. The AUC of the three genera after combining was 0.91 (0.82–0.91, P＜0.001) (Figure 3).

3.2.1. Only altered in the non-antibiotics group

There were 13 genera only altered in the non-antibiotics group, including ten genera with decreased abundance (Bifidobacterium, Collinsella, Phascolarctobacterium, Ruminococcaceae, Haemophilus, Butyricicoccus, Lachnospira, Flavonifractor, Actinobacillus, and Holdemania) and three genera with increased abundance (Propionibacterium, Alloprevotella, and Enterobacter) (Table 2). 46.2% (6/13) of the genera belonged to Firmicutes, 23.1% (3/13) to Actinobacteria, 23.1% (3/13) to Proteobacteria, and 7.7% (1/13) to Bacteroidetes (Supplementary Figure 2A). Gram-positive bacteria accounted for 69.2%, whereas gram-negative bacteria accounted for 30.8% (Supplementary Figure 2B). Among them, the top three genera Bifidobacterium, Collinsella, and Phascolarctobacterium with the greatest decreases in relative abundance were predicted as biomarkers for CCP not receiving antibiotics, and they were not appropriate as biomarkers for cases receiving antibiotics.

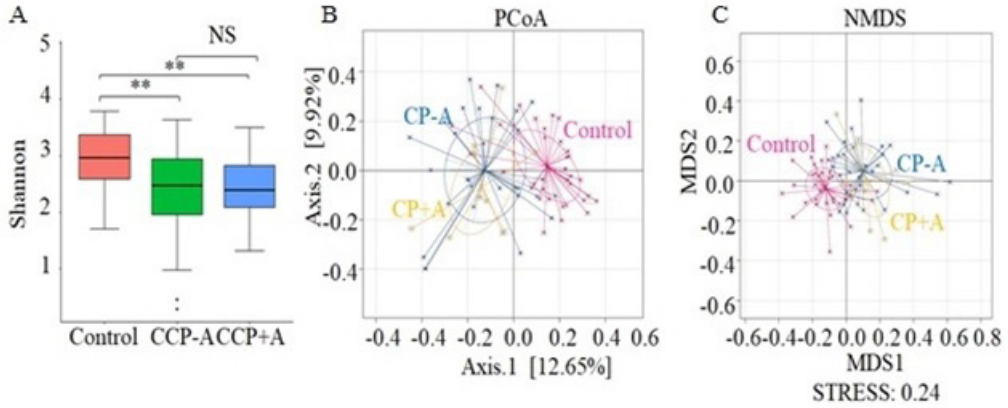


Figure 1: Alterations of the gut microbiota diversity in the antibiotics, non-antibiotics, and control (healthy adolescent participants) groups. (**A**) Alpha diversity in patients and control subjects was calculated using the Shannon index, and a two-tailed Wilcoxon rank-sum test was used for comparisons. **P < 0.01. (**B and C)** Beta diversity in patients and control subjects was calculated using PCoA (principal coordinate analysis) and NMDS (nonmetric multidimensional scaling).

Table 2: Thirteen genera with altered abundance specific to non-antibiotics treated CCP *.

Taxon	Mean, CCP	Mean, Control	SD, CCP	SD, Control	*P* value	*Q* value	Sum of the mean	Difference of the mean
Genera with decreased abundance								
Bifidobacterium	5.384003121	10.00468904	7.112297726	12.81032623	0.024145843	0.172470305	15.38869	-4.62069
Collinsella	0.202506117	2.618743787	0.60738693	7.992463997	0.010846234	0.095702062	2.82125	-2.41624
Phascolarctobacterium	0.114796407	2.493490067	0.325202201	5.427501051	0.002699016	0.031142497	2.608286	-2.37869
Ruminococcaceae	0.668316645	1.46192492	1.068608505	1.520697039	0.001345065	0.020387557	2.130242	-0.79361
Haemophilus	0.01112954	0.706458228	0.041389543	2.168140678	0.00135917	0.020387557	0.717588	-0.69533
Butyricicoccus	0.139425632	0.474183971	0.238831535	0.631325889	0.001045791	0.020387557	0.61361	-0.33476
Lachnospira	0.021009371	0.198249017	0.064028563	0.409616409	0.002019129	0.025239108	0.219258	-0.17724
Flavonifractor	0.081216264	0.197118918	0.154397664	0.347354816	0.022666131	0.169995985	0.278335	-0.1159
Actinobacillus	0	0.003229959	0	0.016553088	0.033866211	0.195381988	0.00323	-0.00323
Holdemania	0.01194294	0.014857003	0.023372649	0.017723333	0.044121667	0.228215518	0.0268	-0.00291
Genera with increased abundance								
Propionibacterium	0.000378658	0.001680236	0.000989336	0.00445396	0.037546309	0.20614368	0.002059	0.001302
Alloprevotella	0	0.044636568	0	0.237420552	0.028124808	0.176505959	0.044637	0.044637
Enterobacter	0.291762281	4.007848302	0.910890091	9.75553311	0.005105145	0.054697987	4.299611	3.716086

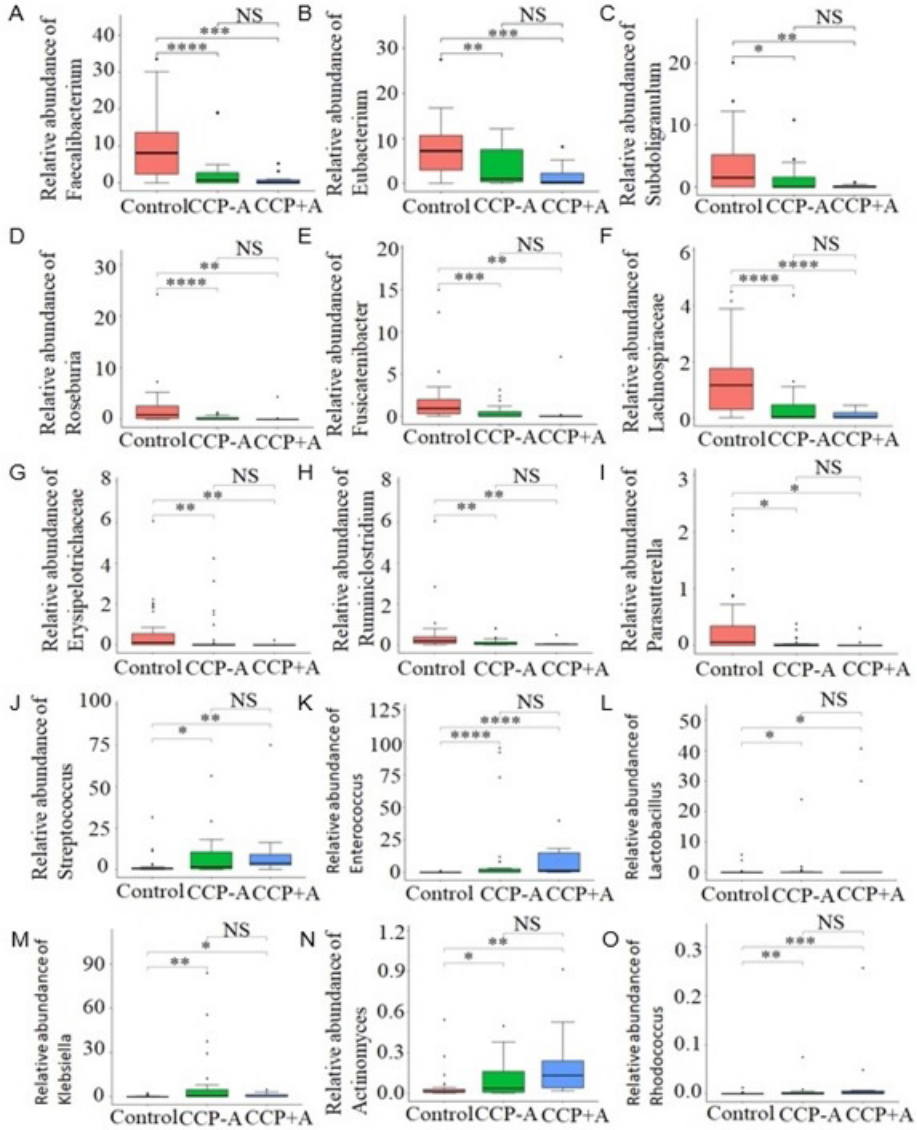


Figure 2 The common abundance altered genera in the antibiotics group (CCP + A) and the non-antibiotics group (CCP − A). (**A–I**) Genera with decreased abundance both in the CCP − A and CCP + A groups compared to the control group. (**J–O**) Genera with increased abundance both in the CCP − A and CCP + A groups compared to the control group of healthy adolescent participants.

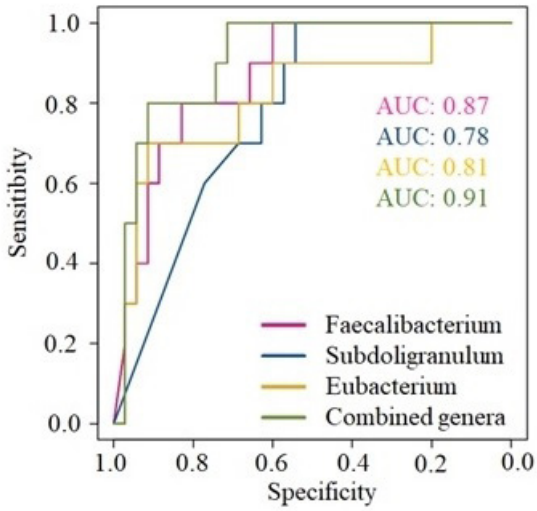
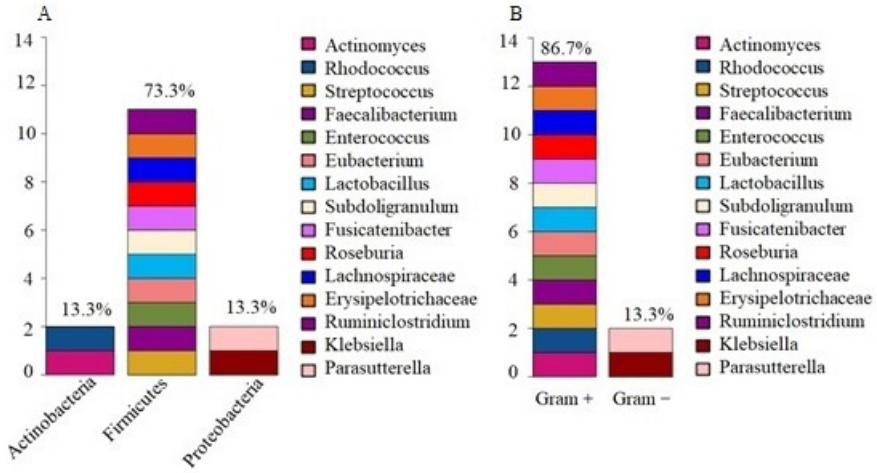
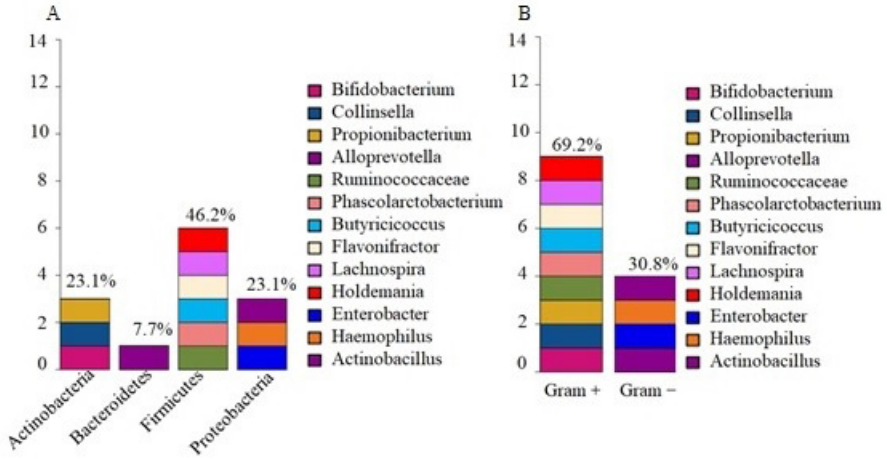


Figure 3: The area under receiver operating characteristics (AUROC) curve analysis of the performance of the top three genera, with the greatest decreases in abundance noted in children with CP treated with antibiotics. *Faecalibacterium*: AUC = 0.87 (0.76–0.87, P＜0.0001), *Subdoligranulum*: AUC = 0.78 (0.65–0.78, P＜0.01), and *Eubacterium*: AUC = 0.81 (0.64–0.78, P＜0.01). The use of each of the three individual arcsine square-root transformed abundance values, along with the coefficients from multivariate logistic regression: AUC = 0.91 (0.82–0.91, P＜0.001).



Supplementary Figure 1: Classification and proportion of the commonly altered genera between the antibiotics and non-antibiotics groups. (**A**) The altered bacteria are classified by phylum. (**B**) The altered bacteria are classified by Gram stain status.



Supplementary Figure 2: Classification and proportion of the specifically altered genera in the non-antibiotics group. (**A**) The altered bacteria are classified by phylum. (**B**) The altered bacteria are classified by Gram stain status.

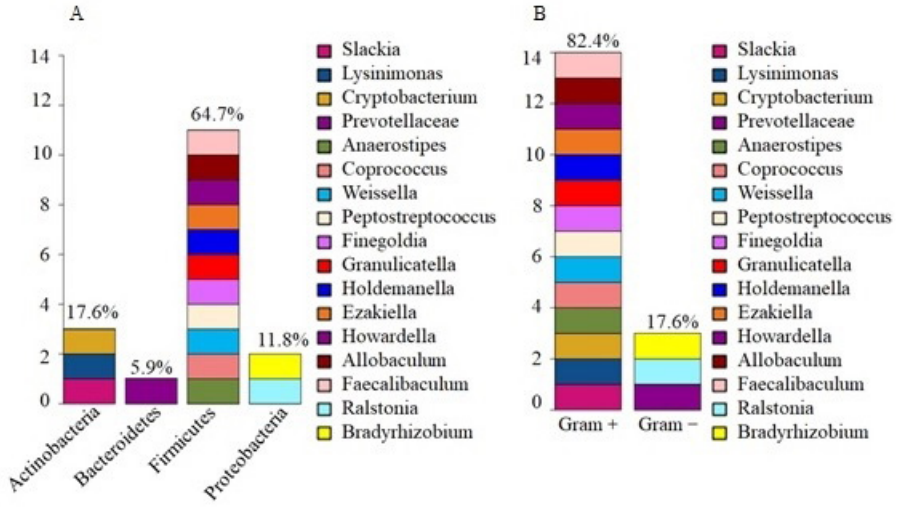
3.2.2. Only altered in the antibiotics group

In addition, there were 17 genera only altered in the antibiotics group, including five genera with decreased abundance (Anaerostipes, Coprococcus, Prevotellaceae, Ezakiella, and Slackia) and 12 genera with increased abundance (Cryptobacterium, Lysinimonas, Bradyrhizobium, Faecalibaculum, Allobaculum, Finegoldia, Ralstonia, Howardella, Peptostreptococcus, Granulicatella, Holdemanella, and Weissella) (Table 3). More than half (64.7%; 11/17) of them belonged to Firmicutes, 17.6% (3/17) to Actinobacteria, 11.8% (2/17) to Proteobacteria, and 5.9% (1/17) to Bacteroidetes (Supplementary Figure 3A). Gram-positive bacteria accounted for 82.4%, whereas gram-negative bacteria accounted for 17.6% (Supplementary Figure 3B). Compared to the 13 genera altered only in the non-antibiotics group, the differences of the genera and the proportion of gram-positive bacteria were not statistically significant (Firmicutes, 64.7% vs. 46.2%, P = 0.310; Actinobacteria, 17.6% vs. 23.1%, P = 1.000; Proteobacteria, 11.8% vs. 23.1%, P = 0.628; Bacteroidetes, 5.9% vs. 7.7%, P = 1.000; Gram-positive bacteria, 82.4% vs. 69.2%, P = 0.400).

Table 3: Seventeen genera with altered abundance specific to antibiotics treated CCP *.

Taxon	Mean, CCP	Mean, Control	SD, CCP	SD, Control	*P* value	*Q* value	Sum of the mean	Difference of the mean
Genera with decreased abundance								
Anaerostipes	0.689955388	2.524318838	1.224037475	4.711537781	0.024296868	0.146753084	3.214274227	-1.834363
Coprococcus	0.017554564	0.421923567	0.034333806	1.011581908	0.016831643	0.105899086	0.439478131	-0.404369
Prevotellaceae	0.002490757	0.049346521	0.002704141	0.157297864	0.006533801	0.065098876	0.051837277	-0.046856
Ezakiella	0	0.003269544	0	0.006828804	0.048520506	0.228956136	0.003269544	-0.00327
Slackia	0.004211841	0.004930168	0.008571489	0.029167269	0.011866891	0.077908717	0.009142009	-0.000718
Genera with increased abundance								
Cryptobacterium	0.000601683	0	0.001326595	0	0.008353829	0.065098876	0.000601683	0.0006017
Lysinimonas	0.001029322	0	0.002225906	0	0.008353829	0.065098876	0.001029322	0.0010293

Bradyrhizobium	0.002310748	8.98388E-05	0.004011584	0.000531493	0.00731893	0.065098876	0.002400587	0.0022209
Faecalibaculum	0.003464665	0.000199503	0.006538333	0.001180273	0.008622368	0.065098876	0.003664167	0.0032652
Allobaculum	0.00458121	0.000133002	0.012358063	0.000786849	0.010129515	0.069525309	0.004714211	0.0044482
Finegoldia	0.01000059	0.000217593	0.017089454	0.000733576	0.000300947	0.007573844	0.010218183	0.009783
Ralstonia	0.010360386	0	0.026364955	0	0.000121421	0.005013734	0.010360386	0.0103604
Howardella	0.012364111	0	0.03811185	0	0.008353829	0.065098876	0.012364111	0.0123641
Peptostreptococcus	0.0218995	0.002889463	0.037331796	0.00820946	0.046117069	0.226471157	0.024788963	0.01901
Granulicatella	0.051668617	0.024873865	0.079854468	0.058269003	0.036943508	0.206199029	0.076542482	0.0267948
Holdemanella	0.043182014	0	0.13590659	0	0.008353829	0.065098876	0.043182014	0.043182
Weissella	0.401071694	0.023889815	1.234115242	0.129658835	0.046494079	0.226471157	0.424961509	0.3771819



Supplementary Figure 3: Classification and proportion of the specifically altered genera in the antibiotics group. (**A**) The altered bacteria are classified by phylum. (**B**) The altered bacteria are classified by Gram stain status.

3.2.3. Systematic analysis of gene function

Analysis of the Kyoto Encyclopedia of Genes and Genomes (KEGG) database indicated that the gut microbiota of the antibiotics group CCP was enriched in the phosphotransferase system and was depleted in the bacterial motility proteins and porphyrin and chlorophyll metabolism (Fig. 4).

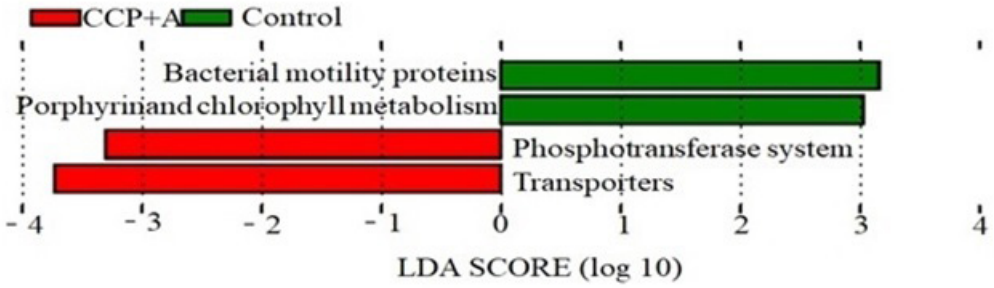


Figure 4 Differences in the functional pathways of the gut microbiota in the antibiotics group (CCP + A) and the control group as analyzed using the Kyoto Encyclopedia of Genes and Genomes (KEGG) orthology (KO). Linear Discriminant Analysis Effect Size (LEfSe) was used for comparison. The predetermined threshold on the logarithmic, linear discriminant analysis (LDA) score for discriminative features was set at >3.0.

4. Discussion

Of the CCP patients who used antibiotic(s) or an oral probiotic drink, this is the first study of the gut microbiota compared to the HCs group. In a recently published study [3]. We compared the gut microbiota of 30 children having CP (non-antibiotics group) with 35 HCs. The participants had not taken any antibiotics or any oral probiotic drink within the previous three months. We identified 28 disordered genera in children with CP not treated with antibiotics compared to HC participants. Among the disordered genera, the six genera with the greatest decreases in absolute abundance were selected as CP biomarkers for the pediatric population: Faecalibacterium, Subdoligranulum, Phascolarctobacterium, Bifidobacterium, Collinsella, and Eubacterium. Our findings further showed that all CCP demonstrated a significantly reduced alpha diversity of the gut microbiota. The top three probiotics of the 15 altered genera in the non-antibiotics and antibiotics groups, i.e., Faecalibacterium, Eubacterium, and Subdoligranulum, demonstrated the greatest decreases in the relative abundance and belonged to the six genera as was predicted previ-

ously by the biomarkers [1]. These demonstrated excellent diagnostic performance (AUC = 0.91), and there were no differences between the non-antibiotics and antibiotics groups, including the alpha diversity of the gut microbiota or the beta diversity of the abundance of genera (Figure 1). These findings show that the main factor affecting gut microbiota is the disease itself and not antibiotics. These findings further supported the hypothesis that the presence of disordered gut microbiota was related to the pathogenesis of CCP, and some gut microbiota may help to identify new biomarkers or therapeutic targets for CP [3] regardless of the antibiotic use status.

Among the remaining 13 genera only altered in the non-antibiotics group, the top three genera with the greatest decreases in relative abundance were not appropriate as biomarkers for cases receiving antibiotics. The effect of antibiotics on the gut microbiota also existed in the findings of the depleting bacterial motility proteins, porphyrin, and chlorophyll metabolism, which indicated that in-depth related research still needs to be carried out (Figure. 2 and 3). In the non-antibiotics group, the gut microbiota were enriched in the phosphotransferase system and depleted in the porphyrin and chlorophyll metabolism. Meanwhile, the altered gut microbiota in the non-antibiotics and antibiotics groups also demonstrated specifically enriched functions. The gut microbiota were specifically enriched in transporters and depleted in bacterial motility proteins in the antibiotics group, and specifically depleted in the ribosomes, starch and sucrose metabolism, and aminoacyl tRNA biosynthesis in the non-antibiotic group (Figure 4). [3]. On the other hand, compared to the 17 genera altered only in the antibiotics group, the differences were not statistically significant in the genera and the proportion of gram-positive bacteria. These findings showed that antibiotics' effect on the gut microbiota of the disease exists but is not significant. This may be because human microbiotas were remarkably resilient and recovered during antibiotic treatment, with transient dominance of resistant bacteroides and taxa-asymmetric diversity reduction [9].

Our study had some limitations. First, only a small number of patients were included. Studies with more patients and the sequencing and comparison of fecal samples during treatment and follow-up would be more useful. Deep sequencing, including metagenomic sequencing, was also necessary. Second, the details of the antibiotics used in each case before admission were not available. We could only make a preliminary estimate based on experience. The top three antibiotics administered in children patients were cephalosporins (43.8%), penicillins (13.2%), and carbapenems (8.7%) [10], which led to changes of gut microbiota in the study. Detailed pre-admission antibiotic use records are still in progress.

In summary, irrespective of the antibiotic receipt status, all CCP had altered diversity and abundance of the gut microbiota. The three of the six identified biomarkers in the previous study (i.e., Faecalibacterium, Eubacterium, and Subdoligranulum) continued to be appropriate for CCP following antibiotic use. Furthermore, the KEGG analysis indicated that the antibiotics caused alterations in the abundance of certain genera and that the enriched functions and the altered gut microbiota in the two groups had their enriched functions. Results showed that the effect of antibiotics on the gut microbiota of the disease does exist, but the effect of disease on gut microbiota is still obvious, which may help diagnosis and further investigation into the pathogenic mechanisms of CP. It reminds us that antibiotics should be used with caution in CCP, even during an acute attack episode, similar to managing pediatric patients with acute pancreatitis [11].

5. Summary points

- Little is known about the effect of antibiotic treatment on the gut microbiota in children with chronic pancreatitis (CCP).
- Our objective was to identify the main gut microbiota genera and characterize these patients' functional mutations after using antibiotics.
- The 16S rRNA sequencing method was used to compare the gut microbiota of healthy controls (HCs) with CCP using and not using antibiotics.
- Our results showed that all CCP demonstrated a significantly reduced alpha diversity of the gut microbiota. The gut microbiota's alpha diversity and the abundance of genera's beta diversity did not show statistical differences between the non-antibiotics and antibiotics groups. The Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis indicated that the antibiotics caused alterations in the abundance of certain genera. The enriched functions and the altered gut microbiota in the two groups had their enriched functions.
- Our results suggest that the use of antibiotics affects the gut microbiota of CCP, but the effect of disease on gut microbiota is still obvious.
- Studies with more patients and the sequencing and comparison of fecal samples during treatment and follow-up would be more useful.

6. Funding

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