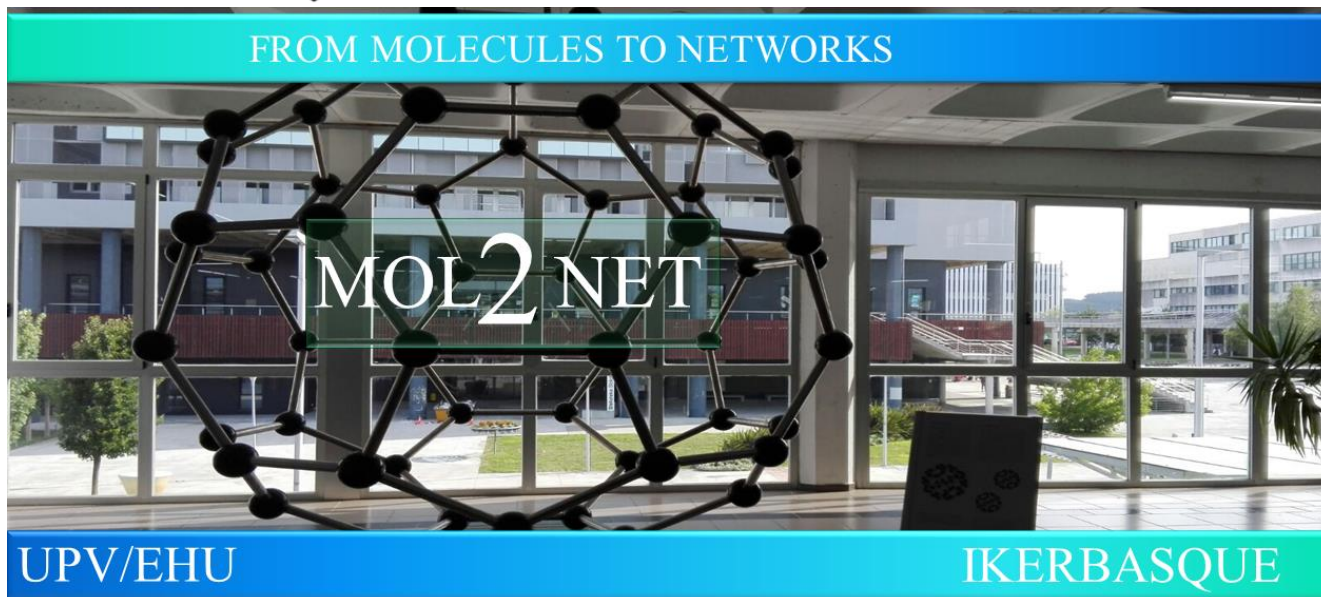




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Effect of antibiotics on gut microbiota in patients with cardiac surgery

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Abstract

Surgical site infection is a common complication after surgery. It is necessary to prevent or treat postoperative infection with antibiotics. The use of antibiotics could disturb the composition and/or functions of gut microbiota. The purpose of the present study was to explore the effect of antibiotics on gut microbiota in patients who underwent cardiac surgery. A total of 622 fecal samples were collected from 244 cardiac surgery patients. The V3–V4 hypervariable region of the bacterial 16S rRNA gene was amplified and sequenced on a MiSeq PE300. The gut microbiota diversity of samples was analyzed from *alpha* diversity at the OTU level and the distribution proportion of dominant bacteria at the genus level by a Circos graph, and the differences among different groups were compared by partial least squares discriminant analysis at the OTU level. As expected, antibiotics could perturb the composition of the gut microbiota in cardiac surgery patients. When antibiotics were administered over 7 days, the

composition of the gut microbiota was significantly disturbed. The gut microbiota composition of patients returning to preantibiotic levels might need antibiotic withdrawal for at least 28 days.

Keywords

Antibiotic, Gut microbiota, Infection, Cardiac surgery

Introduction (*optional*)

Infections are the most common noncardiac complication after cardiac surgery (1, 2). Surgical site infection (SSI) of the sternum is a common complication following cardiac surgery (3). The incidence of SSI in cardiac surgery across a broad range. This complication is associated with an increase in the economic burden, length of hospitalization and mortality (2-6). Infective endocarditis (IE) is a serious disease in the field of cardiology (7, 8). Many bacteria are associated with IE, including *staphylococci*, *streptococci*, and *enterococci*. Effective microbial clearance requires bactericidal antibiotic regimens, usually in combination. Antibiotic therapy, together with cardiac surgery when indicated, is the keystone of treatment for IE, and guidelines recommend that it should be administered intravenously and for a long time (approximately 4-6 weeks) (7-10). The prevention of post cardiac surgery infection remains a major challenge. Clinical practice guidelines for antibiotic prophylaxis provide some recommendations in cardiac surgery (11, 12). Perioperative antibiotics are necessary to prevent infection after cardiac surgery (3-5, 13). The surface and inside of human are covered by a multitude of microorganisms. The majority of microorganisms live in the human gut (14, 15). Recently, the gut microbiota was found to play a critical role in many physiological and pathological processes within in human body. The physiology of almost all organism organs is influenced by the gut microbiota. In particular, gut microbiota could influence the biotransformation of xenobiotics (15, 16). However, the use of antibiotics could disturb the composition and functions of the gut microbiota (15, 17-19). The purpose of the present study was to explore the effect of antibiotics on gut microbiota in patients with cardiac surgery.

Materials and Methods (*optional*)

Patients and sampling

The present study was approved by the Health Authority Ethics Committee of the First Affiliated Hospital of Soochow University and was in accordance with the Declaration of Helsinki. All patients gave written informed consent. Patients underwent cardiac surgery for a variety of reasons, including valvular heart disease, rheumatic valve disease, infectious endocarditis, aortic dissection (Stanford A or B), ascending aortic aneurysm, congenital heart disease, *etc.* These patients were administered antibiotics for the prevention or treatment of infection. The antibiotics used included cephalosporins, sulperazone, tienam, quinolones, meropenem, vancomycin, teicoplanin, *etc.* Fecal samples of patients were collected to analyze the composition of the gut microbiota. Fecal samples were collected before antibiotic administration (preantibiotic group), antibiotic administration over 7 days (postantibiotic group), and antibiotics withdrawal over 7 days (withdrawal-antibiotic group). Fecal samples were collected in a sterile tube

(Sarstedt, Germany), and then stored at -80°C until analysis. The analysis of gut microbiota was detected by Majorbio (Shanghai) Co., Ltd.

Data analysis

The gut microbiota diversity of samples was analyzed from community richness, evenness, diversity and coverage for *alpha* diversity at the OTU level for different groups. *Mann-Whitney U* was used as a statistical test method for *alpha* diversity indexes by GraphPad (version 8.0). The distribution proportion of dominant bacteria in each group of samples, and the distribution proportion of each dominant bacteria in different groups were reflected at the genus level by a *Circos* graph. Partial least Squares discriminant analysis (PLS-DA) was used to compare the differences among different groups at the OTU level. Each group was compared for the differences in gut microbiota in preantibiotic, postantibiotic and withdrawal-antibiotic group by the *Kruskal-Wallis H* test. Then, the 14, 21 and 28 days of antibiotic withdrawal were compared with the preantibiotic group, and it explored how long it took for the gut microbiota to return to the level of preantibiotics. All data were analyzed on the free online platform of the Majorbio Cloud Platform (www.majorbio.com).

Results and Discussion (optional)

Patients' characteristics

A total of 244 cardiac surgery patients, with 622 fecal samples, were enrolled in the present study. The demographic characteristics of the patients, indication of surgery, and drug history were recorded from patients' medical record. All patients were administered any kind of antibiotic for prevention or treatment of infection.

Gut microbiota diversity analysis

The community richness, evenness and diversity are shown in Figures 1-3, respectively. The Ace and Chao index were not significantly different between postantibiotic and withdrawal-antibiotic group, and the simpson even index was not statistically significant difference between preantibiotic and withdrawal-antibiotic group; however, other parameters of *alpha* diversity showed significant statistical differences among the three groups. This was due to antibiotics moving the microbiota to alternative stable states(16). This result indicated that the composition of the gut microbiota might not recover the level of preantibiotic when the antibiotics are withdrawn over 7 days.

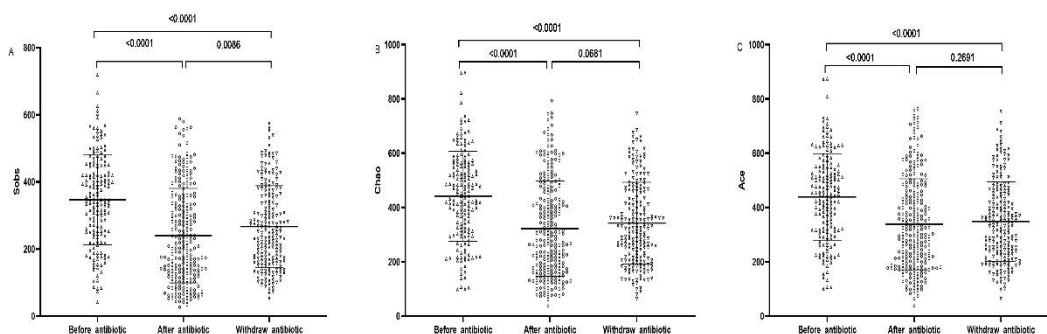


Figure 1. The community richness of each group gut microbiota. A, sobs index; B, chao index; C, ace index.

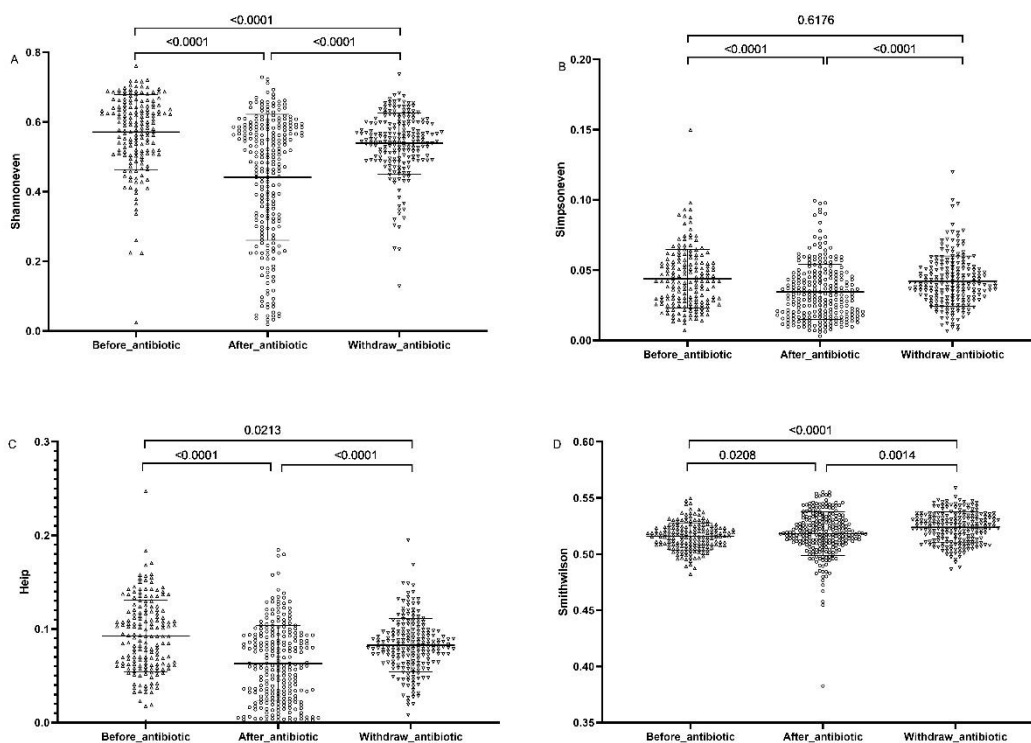


Figure 2. The community evenness of each group gut microbiota. A, shannoneven index; B, simpson even index; C, heip index; D, smithwilson index.

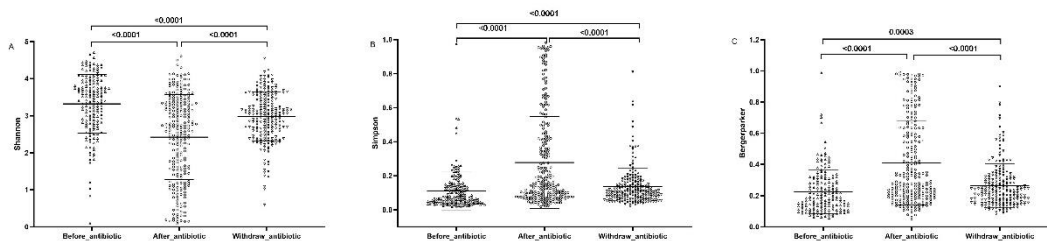


Figure 3. The community diversity of each group gut microbiota. A, shannon index; B, simpson index; C, bergerparker index.

The distribution of dominant bacteria in the sample in each group is shown in Figure 4.

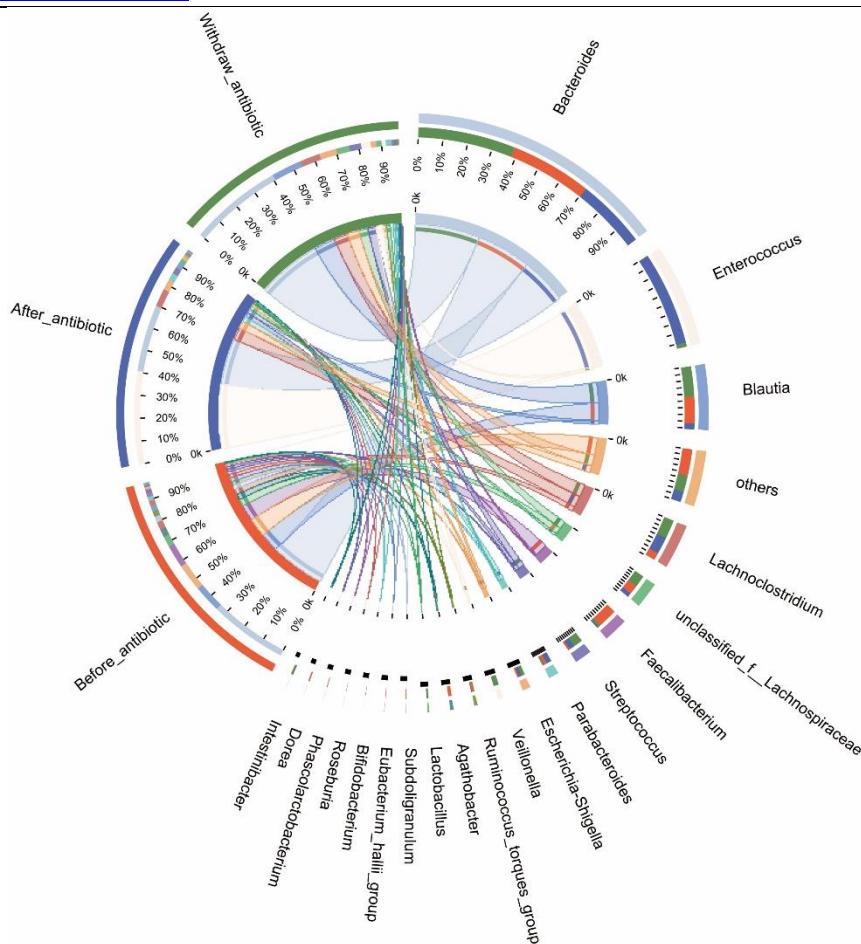


Figure 4. The distribution of dominant bacteria of sample in each group

The PLS-DA result showed that preantibiotic, postantibiotic and withdrawal antibiotic group had some differences in the OTU levels of gut microbiota (Figure 5).

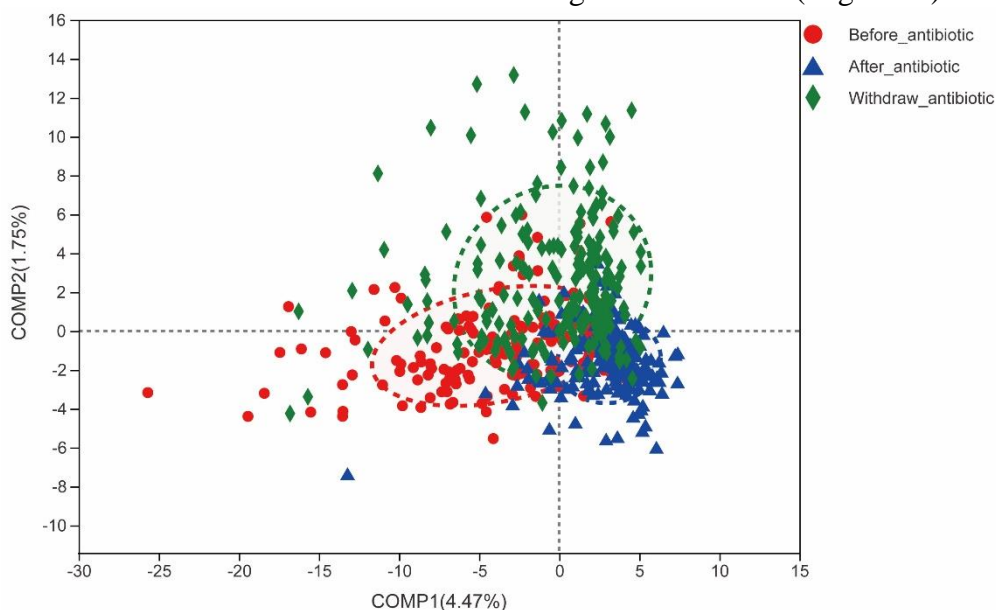


Figure 5. PLS-DA of gut microbiota in each group

The top 20 most abundant bacterial species were compared for species differences by *Kruskal-Wallis H* test for three groups and *Wilcoxon rank-sum* test for two groups at the genus level of gut microbiota (Figure 6).

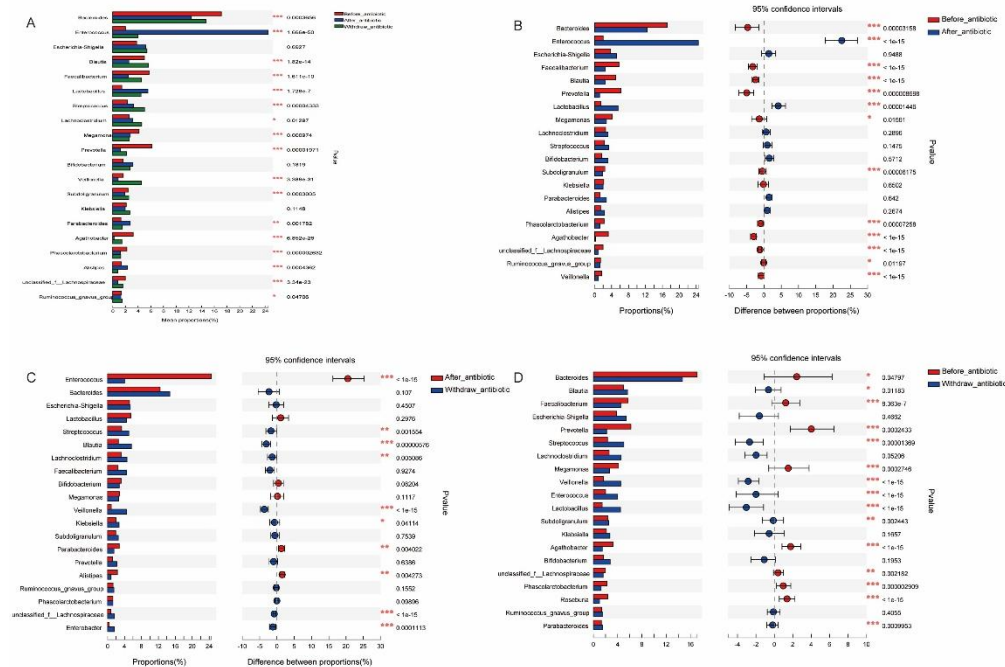


Figure 6. Comparison of the top 20 for abundance of bacterial species. A: three group comparison; B: pre-antibiotics and post-antibiotics; C: post-antibiotics and withdraw-antibiotics; D: pre-antibiotics and withdraw-antibiotics.

After 14, 21 and 28 days of antibiotic withdrawal, the gut microbiota was compared with the preantibiotic group by *Wilcoxon signed-rank* test to explore how long the gut microbiota would recover to the preantibiotic state after antibiotic withdrawal at the genus levels (Figure7). When antibacterial drugs were withdrawn over 14 days, there were still 12 bacterial genera in the top 20 for the relative abundance of bacterial species with statistical differences (Figure 7A); when antibacterial drugs were withdrawn over 21 days, the difference in bacterial genera was significantly reduced (only 4 species, Figure 7B); then, when antibacterial drugs were withdrawn over 28 days, there was no difference in any bacterial genus (Figure 7C). This result indicated that after the patient withdrew antibacterial drugs, it would take at least 28 days for the gut microbiota to recover to the state of preantibiotic, and resilience of the microbiota varies across individuals. The mechanisms for resilience due to feedback (16).

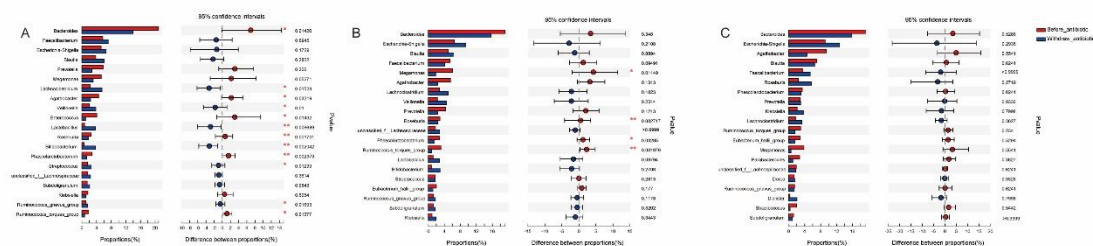


Figure 7. Comparison of the top 20 for abundance of bacterial species for antibiotics withdraw over 14, 21, and 28 days, respectively. A: withdraw-antibiotic over 14 days; B: withdraw-antibiotic over 21 days; C: withdraw-antibiotic over 28 days.

Conclusions (optional)

In conclusion, when antibiotics were administered over 7 days, the composition of the gut microbiota was significantly disturbed. The gut microbiota composition of patients returning to preantibiotic levels might need antibiotic withdrawal over 28 days.

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