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The application of probiotic after antibiotics treatment promotes the recovery of pediatric bronchopneumonia infection

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Abstract. – OBJECTIVE: We aim to investigate the treatment efficacy of combinational applications of oral probiotic with intravenous infusion of antibiotics in pediatric bronchopneumonia infection.

PATIENTS AND METHODS: A total of 76 pediatric patients with bronchopneumonia infection were included in the study. We divided the patients into observation group (n=38) and control group (n=38). The patients in control group received intravenous infusion of antibiotics and symptomatic treatments. In the observation group, in addition to the treatments of the control group, the patients also received oral probiotic. We compared the effective times of treatment, including the durations of wet rale in lung auscultation, cough, fever, and the total time of hospitalization. Additionally, we also recorded the occurrence of adverse reaction, including rash and gastrointestinal reaction. Meanwhile, laboratory tests for systemic inflammation were recorded at different time points.

RESULTS: The durations of rale in lung auscultation (p=0.006), cough (p=0.019), fever (p=0.012), and the total time of hospitalization (p=0.046) in observation group were significantly shorter than those in the control group. The incidence rate of diarrhea was 10.5% (4/38) in the observation group, and 34.2% (13/38) in the control group, with a significantly statistical difference (p=0.013). In the laboratory tests, we found that blood lymphocyte (p=0.034) and high-sensitive C reactive protein (p=0.004) were significantly higher in the control group than that in the observation group at 7th day after the treatments.

CONCLUSIONS: The combinational applications of probiotic and antibiotics in pediatric bronchopneumonia infection were safe and effective and can lower the diarrhea rate.

Key Words:
Bronchopneumonia, Pediatric, Probiotics, Antibiotics, Diarrhea.

Introduction

Pediatric bronchopneumonia is a common respiratory disease among children, which is caused by the invasion of viruses, bacteria, mycoplasma, or other pathogenic microorganisms into the respiratory system[1,2]. Because immune system of children is not mature, they are often unable to resist diseases through their innate immunological responses, especially for those children <5 years old. Generally, without an effective treatment, it is difficult to achieve self-healing[3]. Therefore, a timely and proper therapeutic strategy is essential to promote the recovery of pediatric patients.

In clinic, antibiotic and symptomatic treatment are often needed[4]. However, in recent years, the long-term and irrational use of antibiotic have led to many problems and therefore increasing the potential risks of antibiotic-related complications for children, such as drug resistance, gastrointestinal dysfunction and flora disorder[5-7]. It was previously reported[8] have showed that the incidence rate of diarrhea was about 2.4%-8.0% in the antibiotic-treated pediatric patients with bronchopneumonia. The gastrointestinal dysfunction and flora disorder among children would cause malabsorption of nutrients and other underlying diseases, subsequently influencing the physical development[9].

The function of gut microbiota has been demonstrated to be essential not only in absorption of nutrients, but also in various systemic aspects of human body. Previous literature demonstrated that the gut microbiota was significantly associated with immune system. Estruel-Amades et al[10] found that 70%-80% of immune cells were located in gut associated lymphoid tissue (GALT). The status of the GALT-related immune cells can be regulated with intestinal flora and subsequently influences systemic immunity. In addition, a clinical study also found that combined applications of antibiotics and probiotic shortened

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the recovery time in the patients with diarrhea secondary to pneumonia[11]. However, whether the probiotic assist the recovery through an anti-inflammatory effect is still unclear.

In this study, we applied the combination therapeutic strategy of probiotic and antibiotics in pediatric patients with bronchopneumonia. Given that antibiotic neutralized or prohibited the survival and function of the probiotic, we only selected the pediatric patients with intravenous infusion of antibiotics. This study aimed to observe whether the probiotic can improve the body immunity, so as to promote the recovery of pediatric bronchopneumonia.

Patients and Methods

Patient Information

A total of 76 pediatric patients, ranging from 1- to 8-year-old, with bronchopneumonia were recruited from the Anhui Province Maternity and Child Health Hospital between July 2019 and February 2021. All patients received detailed physical examinations and laboratory tests. The diagnosis of bronchopneumonia was made with two senior doctors according to the symptoms and laboratory indications. The inclusion criteria included 1) the patients with a definite diagnosis of bronchopneumonia and met the treatment standard of antibiotics; 2) the patients aged under 10-year-old; 3) the patients who completed whole course of treatment and laboratory tests. On the other hand, the exclusion criteria were: 1) the patients coincident with diarrhea before treatment; 2) the patients who had severe systemic diseases; 3) the patients who did not meet the treatment standard of antibiotic; 4) the patients aged above 10-year-old; 5) the patients or the immediate family who were not willing to participate the study. Demographic and clinicopathological data at admission were recorded. According to the probiotic application, 38 patients, including 17 males and 21 females, were classified into the control group, who only received intravenous infusion of antibiotics. While, 38 patients, including 16 males and 22 females, were classified into the observation group, who received oral probiotic treatment after 3 days of intravenous infusion of antibiotics.

Treatment Methods

After admission to the hospital, all patients received intravenous infusion of ceftizoxime sodium and erythromycin for 3 days according to the weight of patient. The patients in the observation group received 7-days oral medicine of live *Bacillus Licheniformis* ($>1.0\times10^7$ CFU per capsule) which began after 3 day of intravenous infusion of antibiotics. Other symptomatic treatment methods were applied in both groups with the same treatment protocols to relieve the cough and reduce the phlegm.

Observation of Efficacy

The doctor who checked the treatment efficacy for bronchopneumonia was blinded to the treatment applications. According to the symptoms and results of laboratory tests, we defined the outcomes of treatment as efficiency and inefficiency. The efficiency criteria included: disappearance of symptoms of fever and cough, disappearance of moist rales in lung auscultation, normal levels of C reaction protein (CRP) and highly sensitive CRP (hs-CRP), and normal X ray indication. On the contrary, the inefficiency criteria included no significant relief of symptoms, lung auscultation for pneumonia, CRP level higher than 10 mg/L, and hs-CRP level higher than 4 mg/L.

Statistical Analysis

SPSS software version 19.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. All continuous data were depicted as the mean±standard deviation (Mean±SD) and then analyzed with Student's *t*-test, or as the median with interquartile range (IQR) and analyzed using Mann-Whitney U test. Binary data were analyzed using the Chi-squared test. The *p*-values reported in the study were two-sided and $p<0.05$ was considered significant.

Results

Application of Probiotic Promotes Recovery of Pediatric Bronchopneumonia

We compared the durations of moist rales in lung auscultation, cough, fever, and total time of hospitalization. The results showed that the children in the observation group had significantly shorter durations of moist rales in lung auscultation ($p=0.006$), cough ($p=0.019$), fever ($p=0.012$), and total time of hospitalization ($p=0.046$) than those in the control group (Table I).

Application of Probiotic Reduced the Incidence of Diarrhea

We did not observe the occurrence of rash, which was one of the common side-effects of the antibiotic. However, 4 out of 38 (10.5%) children in the observation group had self-confinement

Table I. Demographic data and effective comparison between groups.

	Total (n=76)	Observation group (n=38)	Control group (n=38)	*p*-value
Age	4.82±2.15	4.55±2.1	5.08±2.16	0.289
Gender (boy)	35 (46.05%)	15 (39.47%)	20 (52.63%)	0.250
Duration of moist rales in lung auscultation (day)	5.08±1.94	4.37±1.57	5.63±1.97	**0.006**
Duration of cough (day)	5.91±2.12	5.34±1.71	6.47±2.35	**0.019**
Duration of fever (day)	3.95±2.04	3.37±1.67	4.53±2.23	**0.012**
Total time of hospitalization (day)	6.91±2.24	6.39±1.62	7.42±2.65	**0.046**
Complication-diarrhea	17 (22.37%)	4 (10.53%)	13 (34.21%)	**0.013**

diarrhea, in comparison to the 13 out of 38 (34.2%) in the control group. The possibility of intestinal infection-related diarrhea was excluded by laboratory tests for stool. The results indicated that the application of probiotic reduced the diarrhea rate after the antibiotic treatment (p=0.013) (Table I).

Probiotic Reduced the High-Sensitive CRP Level

We compared the hematological index of infection between the groups at two time point (admission day and day 7 after admission). The results indicated that most of index recovered to the normal range at day 7. However, the levels of lymphocyte (p=0.034) and hs-CRP (p=0.004) were significantly different between the groups at day 7 after treatment, although the levels of lymphocyte in both group were within the normal range (Table II).

Discussion

In this study, we performed a clinical analysis to investigate the benefit of the oral probiotic application after intravenous infusion of antibiotic in the pediatric bronchopneumonia patients. The results indicated that this therapeutic strategy reduced the general time of hospitalization and promoted the recovery of the pediatric patients. The probiotic alleviated the systemic inflammatory reaction and reduced the occurrence of diarrhea. This study provided a potentially novel treatment option for the pediatric bronchopneumonia patient.

Pediatric bronchopneumonia is a common respiratory infectious disease in children with mild or no obvious symptoms in the early stage of onset. However, it will still cause severe outcomes if not being treated properly[12]. Therefore, a timely and appropriate treatment is the key issue for pediatric bronchopneumonia. Antibiotic is a kind of therapeutic agent and is widely applied in clinical practice to affect the homeostasis of intestinal flora[13]. The application of antibiotic in children combats the systemic inflammatory reaction that is caused by infection and achieves the purpose of effective treatment[14]. However, due to the immaturity of children's immune system, it often leads to some side effects. Among that, the incidence of antibiotic-related diarrhea is commonly observed. Epidemiological results[15-17] showed that the incidence of antibiotic-associated diarrhea among

Table II. Laboratory results of pediatric patients with bronchopneumonia at admission (day 0) and day 7 after admission (day 7). WBC: white blood cell; LNR: lymphocyte-to-neutrophil ratio; hs-CRP: highly sensitive C reactive protein.

	Total (n=76)	Observation group (n=38)	Control group (n=38)	*p*-value
WBC (10^9/L, day 0)	11.22±1.71	11.45±1.62	10.99±1.78	0.242
Neutrophil (10^9/L, day 0)	8.22±0.73	8.36±0.75	8.09±0.69	0.107
Lymphocyte (10^9/L, day 0)	4.20±1.74	4.32±1.50	4.08±1.97	0.551
LNR (day 0)	0.51±0.22	0.52±0.18	0.51±0.25	0.852
hs-CRP (mg/L, day 0)	17.54±4.85	17.70±4.98	17.38±4.78	0.773
WBC (10^9/L, day 7)	7.99±2.42	8.04±2.53	7.95±2.34	0.873
Neutrophil (10^9/L, day 7)	5.47±2.18	5.16±1.73	5.79±2.53	0.210
Lymphocyte (10^9/L, day 7)	3.84±1.70	3.43±1.72	4.25±1.60	**0.034**
LNR (day 7)	0.84±0.57	0.74±0.45	0.94±0.67	0.123
hs-CRP (mg/L, day 7)	2.68±1.27	2.27±1.06	3.09±1.34	**0.004**

Chinese children was generally 11%-62%. The main reason for the diarrhea is that antibiotic destroys the homeostasis of intestinal flora, aggravates the regulation ability of gastrointestinal tract, and causes the decreases of immunity. Trallero et al[18] found combinational application of *Lactobacillus* and *Bifidobacterium* strains was greatly beneficial to the antibiotic-associated diarrhea. This suggested that probiotic might play an important role in maintaining the homeostasis of intestinal flora.

On the other hand, intestinal flora was also demonstrated to play an important part in regulating systemic immune responses. Given 70%-80% of immune cells residing in the GALT, a systemic immune response will be activated to produce a series of inflammatory molecules when the flora is maladjusted[19]. In addition, a study has confirmed that intestinal colonizing bacteria, such as *Escherichia coli, Bacteroides* and *Lactobacillus*, induced the production of regulatory T cells (Treg) in the intestinal lamina propria[20]. Therefore, the imbalance of intestinal flora which is derived from antibiotic application is bound to cause a series of changes in the regulation of the immune system. The imbalance will further increase the burden on children with immature immune system. Therefore, it may be one of the means to promote the recovery of children to balance the body's immunomodulatory response while fighting infection.

In this study, we found that the combinational application of probiotic and antibiotic promoted the recovery of bronchopneumonia in children, shortened the course of the disease, and reduced the incidence of diarrhea. These results suggested that probiotic synergistically promoted the effect of antibiotics in the treatment of bronchopneumonia. We also detected the systemic inflammatory levels between the groups, and the results indicated that probiotic might reduced the systemic inflammatory levels. We hypothesized that this effect might derived from the GALT activation. However, the detailed mechanism should be further discussed in animal models.

Limitations

Some limitations for this study should be carefully concerned. First, we applied *Bacillus Licheniformis* as the therapeutic probiotic in this study because this kind of probiotic with single strain is the most widely applied in clinical practice. However, it still needs laboratory study on the detailed category of dysbacteriosis in gut for the pediatric bronchopneumonia patients. Additionally, pediatric patients received intravenous infusion of ceftizoxime sodium and erythromycin. However, we did not investigate whether oral antibiotics medicine might impact the after-application of probiotics because this intravenous medication might not directly damage the gut microbiota. In our next study, we will investigate whether microbiota composition would influence the outcome of pediatric patients with bronchopneumonia via experiment-based data. Furthermore, we would also augment the sample size in our next investigation to provide more convincing statistical results.

Conclusions

In summary, we found that the therapeutic strategy of combinational application of probiotic and antibiotic can effectively promote the recovery of infection and effectively reduce the occurrence of related diarrhea in pediatric patient with bronchopneumonia.

Informed Consent

Informed consents were obtained from parents o legal guardian of all patients.

Ethics Approval

This study was approved by the Ethics Committee of Anhui Province Maternity and Child Health Hospital (No. YYLL2020-2020FY06-05-01).

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Availability of Data and Materials

The original data of this study is kept by the corresponding authors and can be made available to other researchers upon reasonable request.

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Authors' Contributions

BJL and YMW designed the work. BJL recruited the participants and decided the therapeutic strategy for patients. BJL drafted the manuscript. YMW reviewed and revised the manuscript. All authors approved the publication for the final version.

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None.

Conflict of Interest

The authors declare no conflict of interest.

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