Original Article

Comparison of safety, effectiveness and serum inflammatory factor indexes of *Saccharomyces boulardii* versus *Bifidobacterium* triple viable in treating children with chronic diarrhea: a randomized trial

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Background: Diarrhea is common in children under 5 years of age and is an important public health problem in China. CD is the main obstacle to the growth and development of children, which brings a great burden to individuals, families and society. The objective of this work is to study the efficacy and safety of *Saccharomyces boulardii* versus *Bifidobacterium* triple viable in the treatment of CD in children.

Methods: From October 2018 to October 2020, a total of 161 children aged 2–8 years hospitalized with CD were randomly allocated into *S. boulardii* group, *Bifidobacterium* triple viable group and control group. After 14 days of treatment, the curative effect and recovery time of the three groups were evaluated. The levels of serum interleukin (IL)-6, IL-7 and tumor necrosis factor-alpha (TNF-α) before and after the treatment were valuated and compared among the three groups, together with clinical efficacy and safety.

Results: The recovery time of the *Bifidobacterium* triple viable group was significantly shorter than that of *S. boulardii* group (P<0.05). The marked effective rate and total effective rate of the *Bifidobacterium* triple viable group were significantly higher than those of the control group (P<0.05); the total effective rate of the *S. boulardii* group was significantly higher than that of the control group (P<0.05). The improvement in the levels of IL-6, IL-7 and TNF-α in the *Bifidobacterium* triple viable group was greater than that in the control group; the improvement in IL-6 and IL-7 levels in the *Bifidobacterium* triple viable group was greater than that in the *S. boulardii* group; the improvement in IL-6 and IL-7 levels in the *S. boulardii* group was greater than that in the control group, and the differences were statistically significant (P<0.05)

Conclusions: The efficacy of *Bifidobacterium* triple viable and *S. boulardii* in the treatment of children with CD was better than that of conventional treatment. The treatment effect for *Bifidobacterium* triple viable was more significant, and it was proved to be safe, to shorten the course of disease, and have clinical relevance.

Trial registration: Chinese Clinical Trial Registry ChiCTR2100046444.

Keywords: *Bifidobacterium* triple viable; children; chronic diarrhea (CD); *Saccharomyces boulardii*; serum inflammatory factors

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Introduction

Diarrhea is one of the most important public health problems worldwide. It refers to a gastrointestinal syndrome caused by multiple factors, but characterized by increased frequency of stools and a change in stool characteristics. Diarrhea mainly affects children under 5 years old, especially infants under 2 years old. According to the World Health Organization report in 2017, there are ~1.7 billion cases of diarrhea in children worldwide every year, and ~52,5000 children aged under 5 years die as a result (1). Diarrhea is classified according to the course of disease and can be divided into: acute diarrhea: course of disease <2 weeks; persistent diarrhea: course of disease between 2 weeks to 2 months; chronic diarrhea: course of disease >2 months (2). Diarrhea can cause malnutrition, growth retardation and cognitive impairment in children, and malnutrition can aggravate diarrhea and affect its recovery, thus forming a vicious circle (3). In recent years, with the improvement of living standards and the use of oral rehydration salts, the incidence and mortality of children with acute diarrhea have been significantly reduced. However, the incidence of chronic diarrhea is still high due to complex etiology and difficult treatment, and the patients are mainly children under 5 years old, which seriously affects the growth and development of children. Chronic diarrhea (CD) is generally defined as diarrhea lasting at least 2 weeks (4), and its etiology can be divided into four pathophysiological mechanisms: osmotic, secretory, dysmotility-associated and inflammatory (5).

The etiology of CD in children is complex, because is related to age, diet, climate, living environment, socioeconomic development and genetic factors. In addition to acquired factors, infants can have congenital anatomical abnormalities and congenital genetic diseases. Infection is still the main cause of CD in children, but with improvements in health conditions, the incidence rate of allergic diseases is increasing. The industrialized development of society, tremendous learning pressure and fast pace of life has made the incidence rate of inflammatory bowel disease increase in children.

Saccharomyces boulardii is a nonpathogenic fungal probiotic, which evidence-based medicine has proved has a clear effect on the treatment of acute infection, non-specific diarrhea, antibiotic-associated diarrhea (AAD) and irritable bowel syndrome (6). *S. boulardii* participates in the maintenance of the intestinal microbial barrier by inhibiting pathogenic bacteria, antagonizing the colonizing function, and stimulating intestinal immune and nutritional functions. Moreover, *S. boulardii* can survive in the digestive system for a long time, and is not be destroyed by gastric acid, bile acid or antibiotics. *S. boulardii* can also activate the reticuloendothelial system and complement system;; increase the secretion of human intestinal immunoglobulin (S-IgA); activate the activity of zinc-binding metalloproteinase; improve the secretion of host disaccharidase; improve the absorption function of the host; inhibit the growth and reproduction of intestinal pathogenic microorganisms and the adhesion and invasion of mucosal epithelial cells; release low-molecular-weight protease to neutralize, inactivate and degrade bacterial toxins; alleviate abnormal intestinal secretion;, inhibit the translocation of nuclear factor-kappa B (NF-κB) in the inflammatory signaling pathway; and inhibit the inflammatory signaling pathway, thus playing an anti-inflammatory role (7,8).

Bifidobacterium triple viable bacteria comprises *Bifidobacterium*, *Lactobacillus* and *Enterococcus* to directly supplement the beneficial flora of children's intestines, help restore the normal flora distribution in children, inhibit the growth of pathogenic bacteria, and reduce the absorption of endotoxin by intestinal mucosa (9). Because the intestinal flora is an integral part of the intestinal mucosal barrier, the normal distribution of intestinal flora is also conducive to the recovery of intestinal mucosal barrier function in children (10). Clinical studies have shown that normal intestinal flora can also promote the absorption of nutrients, synthesize vitamins needed for growth and development, and improve immune function, which is conducive to the treatment and rehabilitation of infectious diseases (11). If diarrhea is not treated in time, it can lead to acid-base imbalance, water electrolyte disorder, and even be life-threatening in children (12). Both *S. boulardii* and *Bifidobacterium* are nonpathogenic fungal probiotics that can regulate immune function and intestinal flora, improve host absorption function, alleviate abnormal intestinal secretion, and have anti-inflammatory and antiviral effects. Wang *et al.* (13) found that treatment of acute diarrhea in children with Saccharomyces boulardii combined with *Bifidobacterium* can effectively shorten the duration of diarrhea and hospital stay, reduce the number of diarrhea and enhance the cellular immune function. However, they are rarely used in children with CD (14,15). The purpose of this study was to compare the efficacy of *S. boulardii* and *Bifidobacterium* triple viable in the treatment of children with CD, in order to find an effective, stable and safe microecological treatment, and

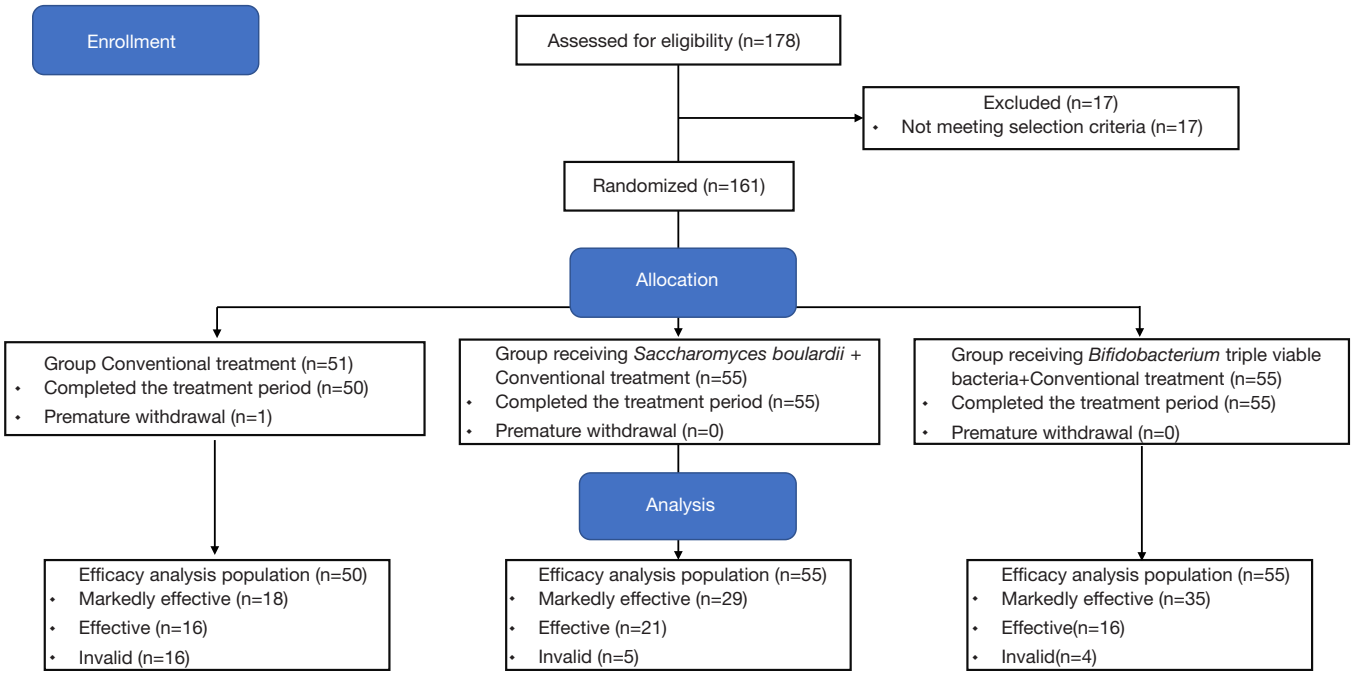

Figure 1 Flowchart of participants through the study of *Saccharomyces boulardii vs. Bifidobacterium* triple viable bacteria in treatment of chronic diarrhea in children.

provide a reference for the clinical treatment of children with CD.

We present the following article in accordance with the CONSORT reporting checklist (available at http://dx.doi.org/10.21037/tp-21-195).

Methods

Setting and study design

This study included 161 children (age, 2–8 years) with CD who were hospitalized in Zhongda Hospital from October 2018 to October 2020. The children were first numbered according to their order of admission, and then divided into three groups using the random number table method by a research physician: *S. boulardii* group (conventional treatment + *S. boulardii*, n=55), *Bifidobacterium* triple viable group (conventional treatment + Bifidobacteria triple live bacteria, n=55), and control group (conventional treatment, n=51). We observed and recorded the recovery time, curative effect, serum interleukin (IL)-6, IL-17, and tumor necrosis factor-alpha (TNF-α) indicators before and after treatment, and the occurrence of adverse reactions in the three groups of children after 14 days, as well as clinical treatment effect and safety. The parents of all study subjects who met the criteria for inclusion gave informed consent. The process is shown in *Figure 1*.

Inclusive criteria: (I) defecation frequency ≥3 times/day and fecal characteristics in accordance with Bristol fecal characteristics types 6 and 7; (II) duration of diarrhea symptoms ≥2 weeks; (III) age 2–8 years; (IV) routine fecal examination without white or red blood cell counts.

Exclusion criteria: (I) mucus stool or pyorrhea; (II) had taken other probiotics, antidiarrheal drugs or drugs affecting gastrointestinal motility within 2 weeks before inclusion in this study; (III) history of allergic reaction to probiotics.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki (as revised in 2013), and has been approved by the ethics committee of Zhongda Hospital Affiliated to Southeast University (No. 20181092).

Medical history

Demographic and medical history data, such as sex, age, height, weight, course of disease, etc. were collected at the time of enrollment. The number of bowel movements and stool characteristics in the week prior to consultation were

recorded as baseline data, and we performed routine stool, blood, and liver and kidney function tests. We also recorded the pretreatment levels of serum IL-6, IL-17 and TNF-α. After 2 weeks of treatment, we again recorded the number of bowel movements and stool characteristics, adverse reactions, and rechecked routine blood, liver and kidney function tests, and serum IL-6, IL-17, and TNF-α levels.

Treatments

The control group was given routine treatments such as oral montmorillonite powder, rehydration salt and intravenous rehydration, while the *S. boulardii* group was given routine treatment and oral *S. boulardii* [Biocodex (France) 0.25 g ×6 bags, batch number: s20150051], and the dosage was selected according to the age of the children as follows. Children >3 years old: one bag twice daily; children <3 years old: one bag once daily. The *Bifidobacterium* triple viable group was given conventional treatment and oral *Bifidobacterium* triple viable capsules (Shanghai Xinyi Pharmaceutical Co., Ltd. specification: each capsule contains 210 mg powder, batch No. Guoyao Zhunzi s10950032). The dosage was selected according to age: children >3 years old, 2 capsules each time, twice daily; children <3 years old, 1–2 capsules each time, twice daily. The powder in the capsule could be administered in warm boiled water. The course of each treatment was 14 days.

Serum inflammatory factors

Before treatment and 14 days after treatment, 5 mL sample of peripheral venous blood from the forearm of each child was drawn, centrifuged at 1,000 g for 15 min, removal of the supernatant for storage at −80 ℃ before testing for changes in serum IL-6, IL-17, and TNF-α levels using a double antibody sandwich enzyme-linked immunosorbent assay [Elabscience (catalog Nos. E-ELN-H0102c, E-EL-H0105c, E- EL-H0109c]. All tests were performed in strict accordance with the manufacturers' instructions.

Efficacy evaluation

According to the Chinese Diarrhea Disease Diagnosis and Treatment Program (16), the curative effect of CD is divided into three types: markedly effective [number of stools returned to normal (≤2 times/day) and stool characteristics returned to normal (Bristol types 3, 4, 5)]; effective [defecation frequency returned to normal after treatment (≤2 times/day) or stool characteristics returned to normal (Bristol types 3, 4, 5]; ineffective, defecation frequency still ≥3 times/day after treatment, and stool characteristics still Bristol classification 6 and 7. The total effective rate (%) = (number of markedly effective cases + number of effective cases)/total number of people ×100%. The recovery time was recorded, and the final evaluation of efficacy was performed on the 14th day of treatment.

Adverse reaction registration

Any adverse reactions during the treatment of all patients were recorded and compared with the blood routine and liver and kidney function tests before treatment.

Statistical analysis

SPSS 22.0 software was used for statistical analysis. The measurement data with a normal distribution was expressed by $\bar{x}\pm s$. The paired *t*-test was used for comparison before and after treatment in the same group, and the *t*-test of independent samples was used for comparison between groups. Chi-square test was used for comparison of count data between groups. $P<0.05$ indicated a statistically significant difference.

Results

Baseline data

A total of 161 patients with CD of various etiologies were included. The main causes were allergic diarrhea (51/161, 31.68%), intestinal infection (71/161, 44.10%), lactose intolerance (21/161, 13.04%) and AAD (26/161, 16.15%); 49 cases (30.43%) had unclear etiology and 112 cases (69.57%) had clear etiology. Among the children with a clear cause, 36 cases were caused by single factor (22.36%), and 76 cases were caused by multiple factors (47.20%). Among them, allergic diarrhea combined with intestinal infection, intestinal infection combined with lactose intolerance, and AAD mainly associated with intestinal infection. Baseline characteristics of the study population are presented in *Table 1*. There were no significant differences in serum IL-6, IL-17, and TNF-α levels among children with CD before treatment ($P>0.05$). The process is shown in *Figure 1*.

Table 1 Baseline characteristics of participants: comparison of treatment groups

Characteristics	Conventional treatment	*Saccharomyces boulardii*	*Bifidobacterium* triple viable bacteria	P value
n	50	55	55	
Age (years ± SD)	4.48±1.88	4.43±1.85	4.25±1.82	0.79
Sex (male/female)	28/22	31/24	31/24	0.99
Height (cm ± SD)	106.7±15.6	109.5±16.8	105.9±17.1	0.67
Diarrhea duration before intervention (days ± SD)	61.3±29.4	58.7±25.9	59.2±28.1	0.73

Table 2 Comparison of efficacy after treatment of patients in three groups

Group	Cases (n)	Markedly effective, n (%)	Effective, n (%)	Invalid, n (%)	Total effective, n (%)
Control group	50	18 (22.0)$^{\#}$	16 (30.2)	16 (30.2)$^{*\#}$	34 (68.0)$^{*\#}$
S Saccharomyces boulardii group	55	29 (35.4)	21 (39.6)	5 (9.1)	50 (90.9)
Bifidobacterium triple viable group	55	35 (42.7)	16 (30.2)	4 (7.3)	51 (92.7)

*, P<0.05 *vs.* the effect of *S. boulardii* group. #, P<0.05 *vs.* the effect of *Bifidobacterium* triple viable group.

Comparison of curative effect

In the control group after treatment, a total of 26 returned to normal defecation frequency (≤2 times/day), 26 had stool properties return to normal, and in 18 cases both returned to normal at the same time, giving an effective rate of 30.2% (16/50), and a markedly effective rate of 22.0% (18/50); in the *S. boulardii* group, there were 39 cases of defecation frequency returning to normal after treatment (≤2 times/day), 40 cases of stool characteristics returning to normal, 29 cases of both returning to normal at the same time, giving an effective rate of 39.6% (21/55), and markedly effective of 35.4% (29/55); after treatment with *Bifidobacterium* triple viable bacteria, there were 43 cases of defecation frequency returning to normal (≤2 times/day), 43 cases of stool characteristics returning to normal, and 35 cases of both recovering to normal at the same time, giving an effective rate of 30.2% (16/55), and a markedly effective of 42.7% (35/55).

There was a significant difference between the control and *Bifidobacterium* triple viable bacteria groups after treatment and the total effective rate (P<0.05); the control and *S. boulardii* groups showed a significant difference after treatment (P<0.05) (*Table 2*).

Comparison of recovery time

The recovery time of the *Bifidobacterium* triple viable group was significantly shorter than that of the *S. boulardii* and control groups, the recovery time of the *S. boulardii* group was significantly shorter than that of the control group, and the difference was statistically significant (P<0.05) (*Figure 2*, *Table 3*).

Levels of IL-6, IL-17 and TNF-α before and after treatment

There was no significant difference in IL-6, IL-17, and TNF-α among the three groups of children before treatment (P>0.05), but after the treatment, all the indicators improved, and the degree of improvement in IL-6, IL-17 and TNF-α levels in the *Bifidobacterium* triple viable group was better than in the control group (statistically significant difference: P<0.05); the improvement in IL-6 and IL-17 levels in the *Bifidobacterium* triple viable group was better than in the *S. boulardii* group (statistically significant difference: P<0.05); the improvement in IL-6 and IL-17 levels in the *S. boulardii* group was better than in the control group (*Table 4*).

Adverse reactions

No serious adverse reactions occurred in any of the groups. In the control group, there was one case of constipation, which disappeared after drug withdrawal. There were no

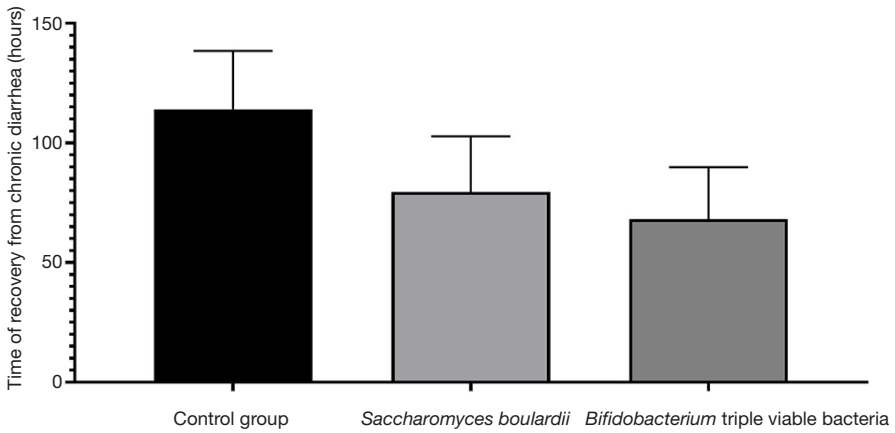

Figure 2 Time of recovery from diarrhea in conventional treatment, *Saccharomyces boulardii* and *Bifidobacterium* triple viable bacteria groups.

Table 3 Comparison of time to recovery after treatment in three groups ($\bar{x}$±s)

Group	Cases (n)	Time to recovery (h)	Max. (h)	Min. (h)
Control group	50	114.04±24.43*#	153	76
Saccharomyces boulardii group	55	79.51±23.25#	131	43
Bifidobacterium triple viable group	55	68.13±21.71	114	22

*, P<0.05 *vs.* the effect of *S. boulardii* group. #, P<0.05 *vs.* the effect of *Bifidobacterium* triple viable group.

Table 4 Changes in inflammatory factors (IL-6, IL-17, TNF-α) of patients in three groups before and after treatment ($\bar{x}$±s)

Group		Cases (n)	IL-6 (pg/mL)	IL-17 (pg/mL)	TNF-α (pg/mL)
Control group	Before treatment	50	26.04±3.30	28.84±5.30	20.02±3.89
	After treatment	50	15.26±3.40*#▲	16.95±2.77*#▲	9.90±2.42*▲
Saccharomyces boulardii group	Before treatment	55	28.123±3.70	28.67±5.00	20.66±3.85
	After treatment	55	12.09±2.08*▲	13.15±1.36*▲	8.96±1.64*
Bifidobacterium triple viable group	Before treatment	55	27.33±3.41	27.95±4.50	20.86±3.56
	After treatment	55	9.44±1.30*	10.15±0.85*	8.33±1.86*

*, P<0.05 *vs.* the levels before treatment. #, P<0.05 *vs.* the levels of *S. boulardii* group. ▲, P<0.05 *vs.* the levels of *Bifidobacterium* triple viable group.

significant differences in routine blood, liver and kidney function tests in the three groups after treatment (P>0.05).

Discussion

Previous studies of probiotics in the treatment of diarrhea have mostly focused on acute diarrhea, viral diarrhea or AAD, and many have confirmed the effectiveness of probiotics for diarrhea symptoms in these cases (17-20). There are many reasons for CD in children in the clinic. In order to investigate whether probiotics are effective for all causes of diarrhea, this study did not limit the cause of CD, but used symptoms as an inclusion criterion. A total of 161 cases of CD with various causes were included. The results showed that probiotics had a better therapeutic effect on the overall symptoms of diarrhea. There were differences

in the number of cases of different causes, and because the number of cases of some causes was too few, this study was unable to group by cause to conduct a comparative analysis.

The pathogenesis of various diseases that cause CD mostly involves the participation of dysbacterial factors. Long-term CD itself can lead to obvious intestinal flora imbalance. Diarrhea and flora imbalance are mutual cause and effect. Studies have shown that by excluding bacterial infection and repeated use of a variety of antibiotics, the number of *Escherichia coli*, *Bacteroides* spp. and Bifidobacteria in the intestines and feces of patients with CD decreased, the number of *Clostridium perfringens* increased, and *Proteus mirabilis*, *Serratia liquefaciens* and *Enterococcus faecium* became the predominant flora in the intestines, which led to changes in the intestinal microecological environment and aggravated diarrhea symptoms (21,22). Therefore, all kinds of CD can be treated with probiotics. At present, studies have also confirmed that probiotics have a good effect on irritable bowel disease and intestinal allergic diseases (23,24).

When infantile diarrhea occurs, the rapid reproduction of harmful flora in the gastrointestinal tract leads to an imbalance of the intestinal flora, which can lead to protracted diarrhea (25). *Bifidobacterium* triple viable is a type of biological agent of intestinal flora, which together with other anaerobic bacteria occupy the surface of intestinal mucosa, form a biological barrier, prevent the colonization and invasion of bacteria, produce lactic acid and acetic acid, reduce the intestinal pH value, inhibit the growth of pathogenic bacteria, improve the intestinal environment, and reconstruct the normal intestinal microecosystem. At the same time, *Bifidobacterium* can inhibit some pathogenic bacteria in children's intestines, correct the imbalance of intestinal flora, promote intestinal peristalsis, and play an antidiarrheal role (26). The digestive system of young children is not fully developed and mature, and the level of digestive enzymes and gastric acid released by the gastrointestinal tract is low, which leads to a decline in the body's resistance and reduces its immune function. Relevant studies (27) have shown that low immune function is an important factor leading to the occurrence and prolongation of diarrhea in children. Strengthening the immune function of the body can promote the control of diarrhea symptoms. Live bifidobacteria can ferment sugars, restore intestinal peristalsis, promote the synthesis of multiple vitamins and biological enzymes, improve the body's absorption of calcium, iron, vitamins and other trace elements, and enhance human immune function. The results of this study showed that the triple live bacteria of *S. boulardii* and *Bifidobacterium* were significantly better than the control treatment in terms of cure time, effect and total effective rate, and that *Bifidobacterium* triple viable treatment effect was superior to *S. boulardii*, suggesting that *Bifidobacterium* triple viable treatment of infantile diarrhea can promote improvement of symptoms and signs, and improve clinical efficacy. Focal inflammatory response is one of the important mechanisms of the occurrence and development of infantile diarrhea. Its occurrence and development are closely related to IL-6, IL-17, TNF-α and other inflammatory factors. Cytokines play an important role in the occurrence and development of enteritis. IL-6 is a lymphokine secreted by T lymphocytes, and promotes the secretion of C-reactive protein, induces the production of acute reactive protein and aggravates the degree of inflammation (24). IL-17 is a cytokine that plays a resistance role in intestinal infection. It can recruit neutrophils at the inflammatory reaction site and play a mediating role against infection. Once children's intestinal flora is in disorder, coupled with low resistance, IL-17 will play a mediating role in intestinal immune and inflammatory reactions, leading to a sharp rise in its level (28). TNF-α is an inflammatory factor secreted by monocyte macrophages, which participates in the immune response and promotes the production of other inflammatory factors (29). Our results showed that after 14 days of treatment, the serum levels of IL-6, IL-17 and TNF-α in the *Bifidobacterium* triple viable group were significantly lower than those in the control group, indicating that *Bifidobacterium* triple viable can significantly reduce the inflammatory reaction, improve the intestinal mucosal barrier function and improve the intestinal flora distribution in children with CD. The intestinal mucosal barrier is an important part of the intestinal defense mechanism, which can prevent pathogens, endotoxin and other harmful substances from entering human tissues and blood circulation, and avoid the aggravation of injury (30).

S. boulardii also had a therapeutic effect on CD, but it was not as obvious as that of *Bifidobacterium* triple viable. In this study the children have good tolerance to *S. boulardii* and *Bifidobacterium* triple viable, and there are no related adverse reactions.

In conclusion, the treatment of CD in children with *Bifidobacterium* triple viable can significantly reduce the serum levels of IL-6, IL-17 and TNF-α, shorten the clinical course and improve the clinical total effective rate, making

it suitable for clinical use.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at http://dx.doi.org/10.21037/tp-21-195

Trial Protocol: Available at http://dx.doi.org/10.21037/tp-21-195

Data Sharing Statement: Available at http://dx.doi.org/10.21037/tp-21-195

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tp-21-195). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki (as revised in 2013), and has been approved by the ethics committee of Zhongda Hospital Affiliated to Southeast University (No. 20181092). The parents of all study subjects who met the criteria for inclusion gave informed consent.

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