

## Synbiotic for Prevention of Antibiotic-Associated Diarrhea in Children: A Randomized Clinical Trial

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### Abstract

#### Introduction:

Antibiotic-associated diarrhea is a common problem in pediatric population. There is growing interest in probiotics, prebiotics and synbiotics for prevention of this complication because of their worldwide availability as dietary supplements. The aim of this study was to assess the efficacy of a synbiotic mixture in prevention of antibiotic-associated diarrhea.

#### Materials and Methods:

In this randomized controlled trial, 218 patients (111 in the synbiotic and 107 in the placebo group) aged 6 months to 14 years with respiratory tract infection and/or otitis media who needed antibiotic treatment in outpatient setting, were enrolled. They received 1 billion Colony Forming Unit of seven probiotics species plus Fructooligosaccharide in form of powder or placebo (matched for size, shape, and volume) for 7 days. Amoxicillin, Amoxicillin-clavulanic acid, cefixime and Azithromycin were the most common drugs used by physicians. Mothers recorded stool frequency and consistency daily for 7 days.

#### Results:

We found no significant difference ( $P > 0.05$ ) in occurrence of diarrhea between synbiotic and placebo groups.

#### Conclusion:

This synbiotic mixture did not appear to reduce antibiotic-associated diarrhea in children. Further studies are needed to investigate the potential benefits of Synbiotics in prevention of this disease.

#### Keywords:

Synbiotic, Antibiotic-Associated Diarrhea, Prevention

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## Introduction

Nowadays antibiotics are administered extensively for treatment of pediatric bacterial infections such as upper respiratory infection and otitis media. Diarrhea occurs in 5-30% of cases and even higher if broad-spectrum antibiotics are used. Some studies have shown the efficacy of probiotics in the treatment or prevention of this complication (1).

According to WHO definition, probiotics are nonpathogenic living microorganisms which have benefit for the host if received in enough amounts. Prebiotics include materials that enhance the proliferation and development of probiotic microorganisms such as fructo- and galacto-oligosaccharides. Synbiotics are combination of pre and probiotics (2). Probiotics have shown therapeutic effects on diarrhea (3-6), irritable bowel syndrome (7-10), inflammatory bowel disease (11), atopic dermatitis (12,13) and allergic diseases(14). The lactobacillus species, seem to be tried extensively in several kinds of diarrhea such as travelers, antibiotic – associated and radiotherapy induced diarrhea (15).

*Saccharomyces boulardii* inhibits adherence of *Clostridium difficile* to intestinal all cells (16) . In a meta analysis performed on 25 randomized clinical trials, more than 50% of the studies showed efficacy of probiotics in prevention of antibiotic associated diarrhea (17).

Some studies showed that using a probiotic mixture might be more effective at reducing gastrointestinal infections but as shown in other studies efficacy of the probiotics mixtures may be reduced by inhibitory effects between different probiotics strains (18).

There are a few trials assessing the role of probiotic mixtures or combination of prebiotic and probiotic (synbiotics) in diarrheal disorders (19). The purpose of this study was to determine the role of a synbiotic mixture in prevention of antibiotic-associated diarrhea.

## Materials and Methods

This randomized, double blind, placebocontrolled trial was carried out between October 2011 and December 2012 in pediatric outpatient clinics, Qaem University Hospital, Mashhad, Iran. Previously healthy children (aged 6 months to 14 years) with respiratory tract infection and /or otitis media (diagnosed by a pediatrician) who had received antibiotics enrolled in the study. The main objective was to evaluate the efficacy of the synbiotic in prevention of antibiotic associated diarrhea (at least 3 loose stools per day during 2 weeks after starting the antibiotic).

Patients were excluded if they had any of the following conditions: chronic underlying diseases, immunodeficiency, probiotic supplementation or antibiotic consumption in the recent 2 months or known case of lactase deficiency and patients in whom fever, bloody diarrhea or vomiting occurred after initiation of antibiotic as above findings are features of infectious gastroenteritis. The patients were randomly divided into two groups (synbiotic group or placebo group) by a random number table sequence. Patients in the synbiotic group received synbiotic containing 1 billion Colony Forming Unit (CFU) of Protexin Restore: a mixture of *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium infantis*, *Lactobacillus bulgaricus* and Fructooligosaccharide (Protexin healthcare, Somerset, United Kingdom), in the form of freeze dried powder twice daily for one week.

The control group received placebo powder without probiotics which was matched for size, shape, and volume of contents and manufactured by the same company, for the same duration.

The powder was dissolved in 10 ml of water and given per oral. Questionnaires were given to mothers. They recorded stool consistency and frequency daily in

this form. They recorded vomiting, bloody diarrhea or any adverse effects if developed which excluded the child from study. Primary outcome measure was the occurrence of antibiotic-associated diarrhea (at least 3 loose stools per day during 2 weeks after starting the antibiotic) and secondary outcome measure was the duration of diarrhea.

One parent of each patient gave a written informed consent.

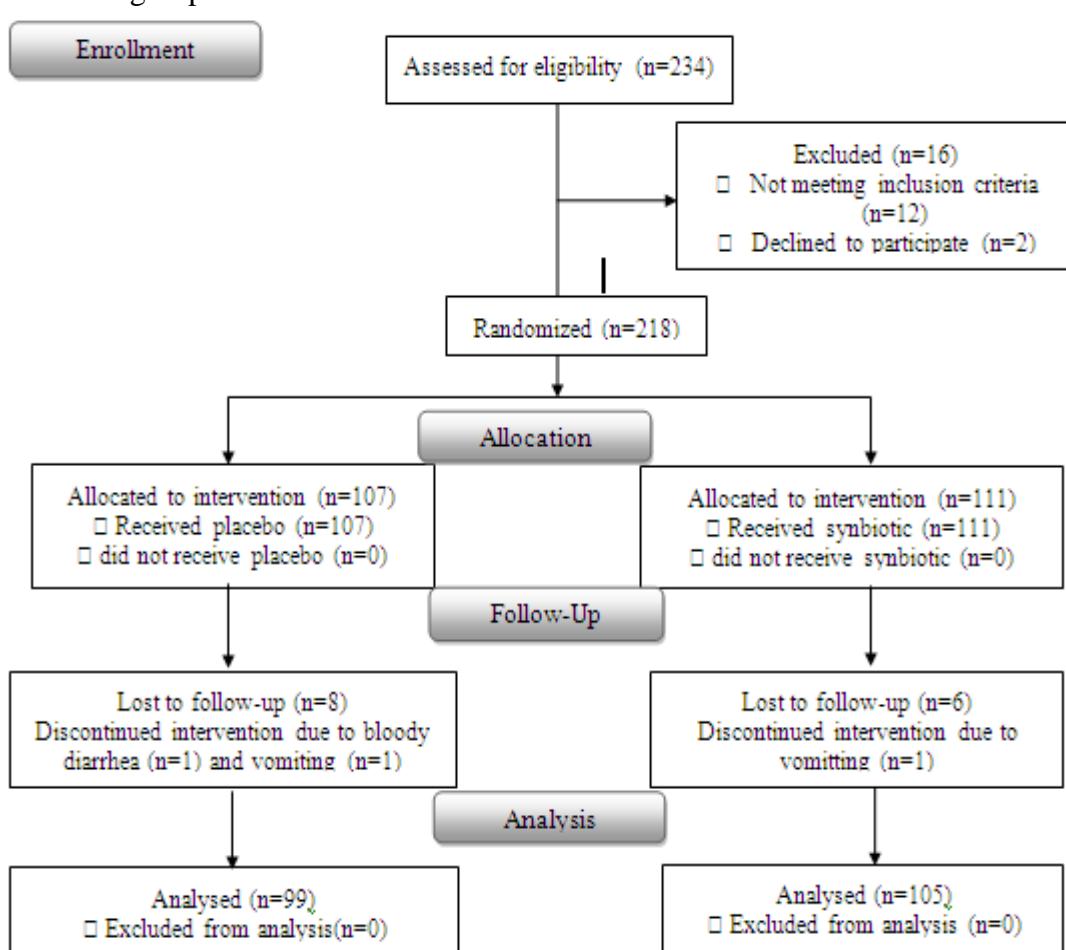
The study protocol was approved by the local ethics committee of Mashhad University of Medical Sciences.

For an  $\alpha$  value of 0.05 and a power level of 80%, the sample size was estimated as 100 Patients in each group.

Chi square test and T student test were used for qualitative and quantitative date respectively.

## Results

Among the totally 234 cases in the study, 16 acquired the exclusion criteria (fever, vomiting or bloody diarrhea) and 218 patients, 111 in the synbiotic and 107 in the placebo group, started the trial. Six patients in Synbiotic group left the study due to loss of follow up (n=5) and vomiting(n=1) and eight patients in Synbiotic group left the study due to loss of follow up(n=6) and, bloody diarrhea(n=1) and vomiting(n=1) (Fig.1).



**Fig.1:** CONSORT Flow Diagram

There was no significant difference in the age, sex, type of the infection or the

administered antibiotics between the 2 groups (Table 1).

**Table1:** Baseline Characteristics of Patients

| Characteristic                    | Probiotic(n=105) | Placebo(n=99) | P     |
|-----------------------------------|------------------|---------------|-------|
| Age(years)                        | 3.37±2.79        | 3.14±2.93     | 0.566 |
| Male/female                       | 59:46            | 53:46         | 0.779 |
| <b>Type of infections</b>         |                  |               |       |
| Pneumonia                         | 25               | 24            | 1.01  |
| Otitis media                      | 25               | 28            | 1.01  |
| Upper respiratory tract infection | 32               | 37            | 1.01  |
| Other infection                   | 23               | 10            | 1.01  |

The most common disorders in which antibiotics were prescribed included pneumonia, otitis media and other upper respiratory infections. Amoxicillin, Amoxicillin-clavulanic acid, Cefixime, Azithromycin and Penicillin were the

antibiotics used in this study (Table1) . Twenty cases in synbiotic group and 24 cases in placebo group had three or more stooling per day. Seventy four and 64 cases in synbiotic and placebo group had loose stool, respectively (Table.2).

**Table.2:** Stool Charactrestics of Patients.

| Outcome                         | Synbiotic(n=105) | Placebo(n=99) | P     |
|---------------------------------|------------------|---------------|-------|
| <b>Stool Consistency</b>        |                  |               |       |
| Looseness                       | 74               | 64            | 0.374 |
| No change                       | 31               | 35            | 0.347 |
| <b>Stool Frequency</b>          |                  |               |       |
| ≤ 3 times per day               | 85               | 75            | 0.290 |
| ≥ 3 times per day               | 20               | 24            | 0.290 |
| <b>Diarrhea Duration (days)</b> | 0.58±1.048       | 2.69±1.58     | 0.637 |

Data are expressed as mean± SD or otherwise stated.

Differences in consistency and frequency of stool and diarrhea duration (days) between two groups were not statistically significant (Table2).We encountered no adverse effects (allergic reactions, sepsis, vomiting) following use of synbiotic in this study.

## Discussion

Ancient Middle East physicians had prescribed yogurt for curing disorders of the intestines and stimulation of appetite and consumption of sour milk had linked to longevity of Abraham in an old Persian Testament (20). Probiotic yogurt shortened the duration of viral diarrhea and hospital stay (5).

As mentioned, in this study synbiotic had no significant effect on minimizing diarrhea, loose stool or stool frequency. Some studies have shown that synbiotic can reduce the duration of diarrhea (21), length of hospital stay and health care cost in acute diarrhea (22,23). There are several published clinical trials that demonstrate beneficial impact of probiotics in prevention of antibiotic -associated diarrhea (1,17,24-27). However, some studies couldn't show these results (28,29). In a recent Cochrane meta-analysis, 16 randomized, parallel, controlled trials in children (up to 18y) were analyzed. Despite the heterogeneity in probiotics strain, dose and duration, as well as study quality, the

overall evidence suggests a protective effect of probiotics in preventing antibiotic-associated diarrhea. Although this analysis indicates that high dose probiotic(>5 billion CFUs/day) is more effective than low dose (<5 billion CFUs/day) (30). In comparison to this Cochrane meta-analysis, we have used low dose probiotics (2 billion CFUs/day) but of the similar strains (*Lactobacilli* spp, *streptococcus* spp and *Bifidobacterium* spp).

To our knowledge there is no study evaluating the effects of synbiotic on antibiotic-associated diarrhea but, regarding to prebiotics-probiotics synergistic effects and positive effects of synbiotics on acute diarrhea, it is possible that synbiotics have beneficial effects on antibiotic-associated diarrhea. The therapeutic effects of synbiotics depend on type of probiotic strains, single-strain or multi-strain, dosage, duration of intervention, study population and environmental background. These variables are the main causes of different results in clinical trials (14).

#### Limitations for this study:

1. Stool quality was observed and recorded by the mothers and it can affect on the reliability of our results.
2. We did not follow the children enough, as we know antibiotic-associated diarrhea can occur during or weeks after antibiotic exposure (31).

Other reasons for difference in effects of synbiotic in these studies may include sample size, genetic factors, and finally, technical differences in the measurements.

#### Conclusions

Although we confirmed the safety and tolerability of synbiotics in this trial, we could not show any benefit of this synbiotic mixture in prevention of antibiotic-associated diarrhea. Future trials with different probiotic, probiotic strains and mixtures are needed to find the best choices in prevention of this common problem. This

study is registered in Iranian Registry of Clinical Trials (IRCT) ID: IRCT 201205229828N1

**Conflict of Interest:** The authors have no conflict of interest.

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