Meta-analysis of the effects of *Bifidobacterium* preparations for the prevention and treatment of pediatric antibiotic-associated diarrhea in China

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ABSTRACT

Bifidobacterium preparations are increasingly used for pediatric antibiotic-associated diarrhea (AAD) in China. The aim of this study was to review existing evidence on the efficacy of *Bifidobacterium* preparations for the prevention and treatment of pediatric AAD in China. Searches were performed with Medline, Embase, Cochrane Central Register of Controlled Trials, CNKI, and CBM databases. Thirty trials met the inclusion criteria. Of the 30 trials, five *Bifidobacterium* preparations were included. The preparations were all *Bifidobacterium* based, in combined with *Lactobacillus*, *Enterococcus*, *Bacillus*, *Streptococcus* or *Clostridium* strains. The pooled results of the 30 trials, which included 7225 participants, indicated a statistically significant association of *Bifidobacterium* preparations administration with reduction in pediatric AAD (odds ratio [OR], 0.33; 95% confidence interval [CI], 0.29–0.39; P < 0.01). When the meta-analysis was re-performed according to the trials explicitly aiming to prevent or treat pediatric AAD, respectively, the pooled results were similar (*Bifidobacterium* preparations use for preventing pediatric AAD (n = 21): pooled OR, 0.34, 95% CI, 0.28–0.41, P < 0.01; *Bifidobacterium* preparations use for treating pediatric AAD (n = 9): pooled OR, 0.32, 95% CI, 0.23–0.43, P < 0.01). Subgroup analyses which based on *Bifidobacterium* preparations variety, clinical condition, or participant's age also showed statistically significant benefit of adjunct *Bifidobacterium* preparations for the prevention and treatment of pediatric AAD in China. The pooled evidence suggested that *Bifidobacterium* preparations might be efficacious for the prevention and treatment of pediatric AAD in China.

1. Introduction

Antibiotics have an important role in the treatment of pediatric infectious diseases. However, the rational of antibiotics use was not seriously considered in China in the past. In 2010, one study analyzed the use of antibiotics for children from 2004 to 2009 in China, and revealed that 85% of children in the study population had been given at least one prescription for antibiotics in 2004–2009.[1] The use of antibiotics disturbs the gastrointestinal flora and causes a range of clinical symptoms, most notably diarrhea. The symptoms range from mild and self-limiting to severe, and antibiotic-associated diarrhea (AAD) is an important reason for non-adherence with antibiotic treatment. The term probiotic refers to a product or preparation containing viable microorganisms thought to be sufficient to alter gastrointestinal flora

and thereby exert beneficial effects.[2,3] Probiotics might maintain or restore gastrointestinal microecology during or after antibiotic treatment through competition of receptor or nutrients, inhibition of epithelial and mucosal adherence, introduction of lower pH, stimulation of immunity, or production of antimicrobial substances.[4,5]

One previous meta-analysis assessed the efficacy of probiotics for the prevention of pediatric AAD, with the combined results in favour of probiotic co-administration with antibiotics.[6] Many clinical trials have also assessed the efficacy of probiotics for the prevention and treatment of pediatric AAD in China. The majority of probiotics used in these trials were *Bifidobacterium*-based interventions in combination with other genera. The purpose of this study was to perform a meta-analysis to examine whether *Bifidobacterium*-based interventions are effective for the prevention and treatment of pediatric AAD in China.

Fig. 1. Study selection flow diagram.
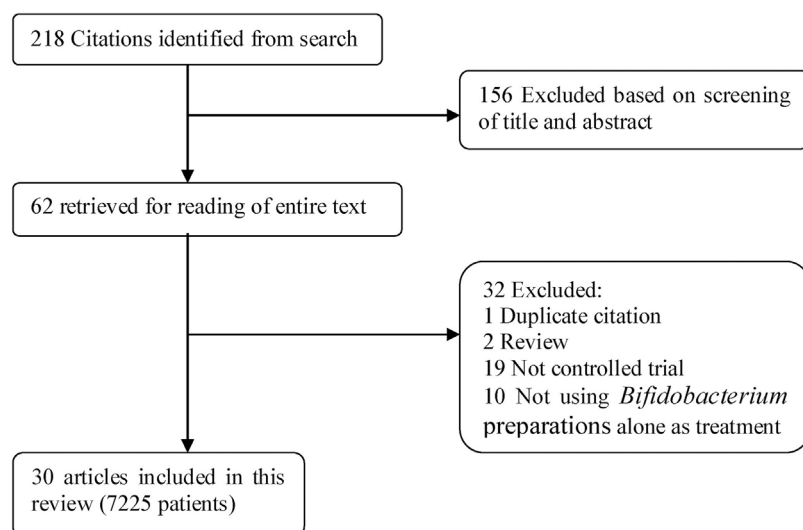
2. Methods

In general, the methods used for this review followed current practices for conducting systematic review and meta-analysis of the literatures.[7] This meta-analysis was completed in accordance with the Quality of Reporting of Meta-analyses statement.[8]

2.1. Search strategy and selection criteria

The following electronic databases were retrieved and no language restriction was applied:

1. WANGFAN (wangfan database, 1990 to December 2016)
2. CBM (China BioMedical Literature Database, 1979 to December 2016)
3. CNKI (China Knowledge Resource Integrated Database, China academic journals, conference proceedings, and theses; 1979 to December 2016).
4. EMBASE (1980 to December 2016)
5. MEDLINE (1966 to December 2016)
6. The Cochrane Central Register of Controlled Trials (1991 to December 2016)

The common search strategy in the study is listed as below, and Chinese language database was retrieved with similar search strategy.

1. clinical trial.mp
2. clinical study.mp
3. efficacy.mp
4. effectiveness.mp
5. 1 OR 2 OR 3 OR 4
6. random$.mp
7. children.mp
8. infant.mp
9. pediatric.mp
10. 7 OR 8 OR 9
11. *Bifidobacterium* $.mp
12. *Peifeikang*.mp
13. *Siliankang*.mp
14. *Jinshuangqi*.mp
15. *Beifeida*.mp
16. *Changlekang*.mp
17. 11 AND12 OR 13 OR 14 OR 15 OR 16
18. Diarrhea.mp
19. Diarrhoea.mp
20. 18 OR 19
21. 5 AND 6 AND 10 AND 17 AND 20

Two reviewers (H.-B.X. and R.-H.J.) selected articles in the following two stages: titles and abstracts, and then full-text articles. Discrepancies between the two reviewers were resolved by consensus or through discussion with a third reviewer (H.-B.S.). The ratings given by the two reviewers were in complete agreement.

2.2. Selection of studies

Trials which included in the present meta-analysis had to meet the following selection criteria: 1. Trials claimed as random allocation; 2. Trials that compared *Bifidobacterium* preparations use as adjunct antibiotic treatment with a concurrent control group receiving only antibiotic treatment; 3. Articles written in either English or Chinese language; 4, at least 10 patients in each group. When two or more articles reported the same data, the most recently updated data were included. References of the identified articles were also checked and principal investigators were asked if they were aware of other trials. Trials of prevention as well as treatment of pediatric AAD were included. This analysis used each study's original definition of diarrhea, which ranged from uncomplicated diarrhea to severe diarrhea with complications such as watery stool, stool consistency, and physician-defined diarrhea.

2.3. Data extraction and quality assessment

Two reviewers (H.-B.X. and R.-H.J.) performed data extraction for all articles and a third reviewer (H.-B.S.) independently performed data extraction for one-third of the articles to assess accuracy in the data extraction. For each study, the following key information was extracted: first author, publication year, study design, patients' demographic characteristics, sample size, adverse effects, and outcomes. The primary outcome was the number of participants with diarrhea in each treatment group. The methodological quality of the included trials was assessed using the Jadad scale for: (1) randomization, (2) double-blinding, (3) description of withdrawal, (4) description of randomization, (5) description of blinding. Trials scoring 1 or 2 points are considered low quality; trials scoring 3–5 points are considered high quality.[9] In addition, these two reviewers also evaluated the internal validity of the trials with an 11-item scale developed by Cochrane Back Review Group.[10]