EVIDENCE-BASED CASE REPORT

The Efficacy of Probiotic in Adults with Acute Infectious Diarrhea

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Abstract

    Diarrhea is a global health problem with high morbidity and mortality. In developing countries, acute diarrhea is most commonly caused by infectious pathogens. Regardless of the cause, diarrhea is primarily treated by fluid replacement therapy to decrease the risk of dehydration and death, although it does not affect the duration of diarrhea. Probiotics are able to shorten the duration of diarrhea in children, but its efficacy in adults is unclear. This study aimed to evaluate the benefit of probiotic in reducing the duration of acute diarrhea in adults as compared to placebo. Systematic search was done using four databases: PubMed, Scopus, ProQuest, and Embase, without limit on the year of publication. Randomized clinical trials were selected as the appropriate study design to answer the clinical question and two studies were considered relevant for appraisal. In conclusion, probiotics could improve the recovery of acute infectious diarrhea in adults (level of evidence 1b) however more studies should be carried out since only very few strains of probiotics have been investigated.

Keywords: *probiotics, treatment efficacy, acute diarrhea, adults.*

Efektivitas Probiotik pada Orang Dewasa dengan Diare: Sebuah Laporan Kasus Berbasis Bukti

Abstrak

    Diare merupakan masalah kesehatan global dengan angka morbiditas dan mortalitas yang tinggi. Di negara berkembang, diare akut biasanya disebabkan oleh infeksi. Terlepas dari penyebabnya, tata laksana utama diare adalah terapi rehidrasi untuk mengurangi dehidrasi dan kematian walaupun hal tersebut tidak memengaruhi durasi diare. Probiotik dapat memperpendek durasi diare pada anak-anak, namun efektivitasnya pada orang dewasa masih belum jelas. Tujuan penelitian ini adalah untuk mengevaluasi efek probiotik dalam mengurangi durasi diare akut pada orang dewasa dibandingkan plasebo. Pencarian sistematik dilakukan pada empat database: PubMed, Scopus, ProQuest, dan Embase, tanpa membatasi tahun publikasi penelitian. Randomized clinical trial dipilih sebagai desain penelitian yang tepat untuk menjawab rumusan masalah dan dua penelitian dianggap relevan untuk ditelaah. Disimpulkan bahwa probiotik dapat mengurangi durasi diare akut akibat infeksi pada orang dewasa, namun perlu penelitian lebih lanjut karena hanya sedikit galur probiotik yang sudah diteliti.

Kata kunci: *probiotik, efektivitas pengobatan, diare akut, dewasa*

Introduction

Diarrhea is defined by the WHO as three or more loose or watery stools in a 24-hour period and is termed acute diarrhea if it lasts less than 14 days.[1] As one of the most common gastrointestinal (GI) illnesses, diarrhea is a major health burden, causing approximately 1.78 million deaths (3.7% of total deaths) in low and middle-income countries in 2001 and most of these deaths occurred in children under five years of age.[2] In developing countries, acute diarrhea often occurs due to infection, where more than 20 viruses, bacteria, and parasites are associated with.[3,4]

Irrespective of the cause, diarrhea is mainly treated by fluid replacement therapy to decrease the risk of dehydration and death although it is ineffective in shortening the duration of diarrhea.[5] Diarrhea is usually self-limiting without the need for antibiotics and does not cause complications, however it may cause considerable discomfort that leads to loss of work and disturbance of social activities. As such, novel treatments that can reduce the duration of diarrhea are required.

WHO defined probiotics, as the live microorganisms that yield a health benefit on the host when given in adequate amounts. Probiotics have been shown effective in shortening the duration of diarrhea and in reducing stool frequency in children. [6,7] Whether similar benefits are present in adults, it is uncertain since few studies have been conducted in adults. Therefore, the aim of this study is to evaluate the efficacy of probiotic in adults with acute diarrhea through appraising existing medical evidences.

Case Illustration

An eighty year-old male Indonesian came to a public hospital in Tangerang due to diarrhea since five days prior to admission. The patient approximately had five times of diarrhea per day, with liquid consistency, no blood, and not rice-water-like appearance. There was no vomiting or abdominal pain, but the patient felt weak, nausea, and thirsty. Physical examination and routine blood tests were within normal limits and the patient was diagnosed with acute diarrhea with mild-moderate dehydration. After three days of inpatient care with supportive fluid therapy, the patient's condition had improved favorably and thus was discharged.

Clinical Question

Is there any benefit of giving probiotic to adults with acute infectious diarrhea?

Methods

A comprehensive computer-based literature search was performed using the electronic databases PubMed, Scopus, ProQuest, and Embase on February 2016. The search included Boolean combinations (AND, OR) of the following keywords: *probiotic/ Bifidobacterium/ Enterococcus/Lactobacillus/Saccharomyces/ Streptococcus, treatment/ therapy efficacy/ effectiveness, acute diarrhea/gastroenteritis, adults*. Limits of the search included *'English', 'humans', 'full text available',* and *'adult'*. Year of publication was not limited. Multiple searches followed by manual screening of titles and abstracts were conducted to ensure that all the relevant studies were identified. Reference lists from the articles retrieved were manually assessed to identify additional relevant trials. The methodological quality and critical appraisal of the included studies were independently assessed using the Oxford model of evidence-based medicine.

Results

The literature search using the combinations of keywords and limits as mentioned above initially showed a total of 1.567 studies (Table 1), in which 1.478 of them were considered irrelevant based on their title or abstract, thus were excluded (Figure 1). The remaining 89 studies were screened for double results, yielding 81 potentially relevant papers. Finally, 2 studies were included for critical appraisal following full text reading.

Table 1. Paper Search Terms and Results from Each Database

| Databases	Search terms	Findings	Used
PubMed	(probiotic OR Bifidobacterium OR Enterococcus OR Lactobacillus OR Saccharomyces OR Streptococcus) AND (treatment OR therapy) AND (efficacy OR effectiveness) AND (acute diarrhea OR gastroenteritis)	104	1
Scopus	(probiotic OR Bifidobacterium OR Enterococcus OR Lactobacillus OR Saccharomyces OR Streptococcus) AND (treatment OR therapy) AND (efficacy OR effectiveness) AND (acute diarrhea OR gastroenteritis)	690	1
ProQuest	(probiotic OR Bifidobacterium OR Enterococcus OR Lactobacillus OR Saccharomyces OR Streptococcus) AND (treatment OR therapy) AND (efficacy OR effectiveness) AND (acute diarrhea OR gastroenteritis)	278	0
Embase	(probiotic OR Bifidobacterium OR Enterococcus OR Lactobacillus OR Saccharomyces OR Streptococcus) AND (treatment OR therapy) AND (efficacy OR effectiveness) AND (acute diarrhea OR gastroenteritis)	495	0
	Total	1,567	2
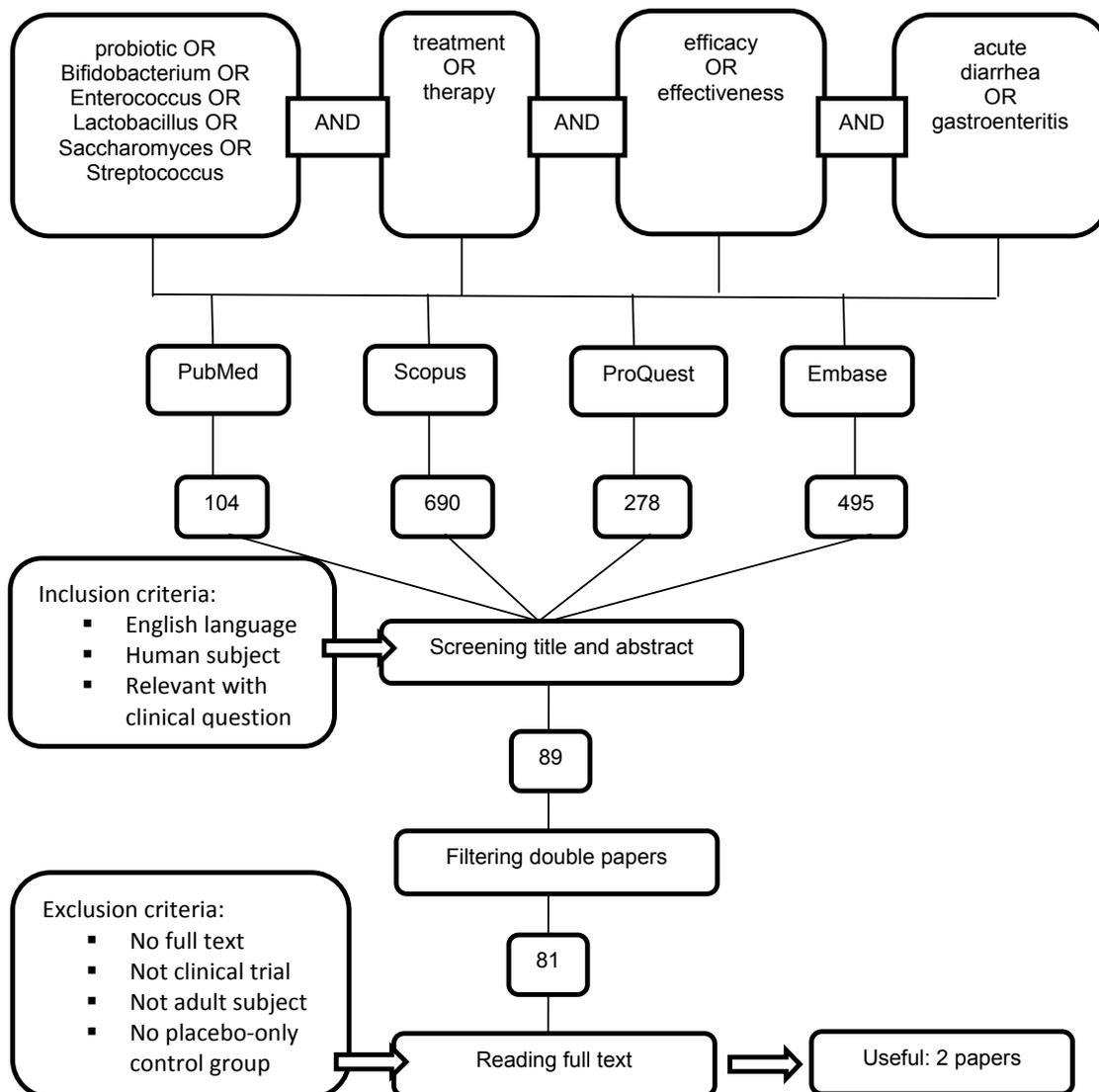
Figure 1. Flowchart of the Searching Methods

Two relevant studies, Buydens et al[8] and Wunderlich et al[9] were critically appraised using oxford's standardized validity, importance, and applicability assessments for therapy studies (Table 2, Table 3, and Table 4). For the calculation of event rates in the assessment of importance (Table 3), an event is defined as diarrhea lasting ≥4 days, whereas non-event is defined as diarrhea lasting <4 days. Description of each study is summarized in Table 5.

Table 2. Assessment of Validity

Validity	Buydens et al	Wunderlich et al
Was the assignment of patients to treatments randomized?	☐	☐
Were the groups similar at the start of the trial?	☐	☐
Aside from the allocated treatment, were groups treated equally?	☐	☐
Were all patients who entered the trial accounted for? – and were they analyzed in the groups to which they were randomized?	☐	☐
Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?	☐	☐

Table 3. Assessment of Importance

Importance	Buydens et al	Wunderlich et al
CER	0.15	0.41
EER	0	0.15
RR	0	0.37
ARR	0.15	0.26
RRR	1	0.63
NNT	6.67	3.85

CER: control event rate; EER: experimental event rate; RR: relative risk;

ARR: absolute risk reduction; RRR: relative risk reduction; NNT: number needed to treat

Table 4. Assessment of Applicability

Applicability	Buydens et al	Wunderlich et al
Is my patient so different to those in the study that the results cannot apply?	☐	☐
Is the treatment feasible in my setting?	☐	☐
Will the potential benefits of treatment outweigh the potential harms of treatment for my patient?	☐	☐

Table 5. Description of the Studies

Description	Buydens et al	Wunderlich et al
Methods	Double-blind, randomized controlled trial in 2 centers in Belgium.	Double-blind, randomized controlled trial in 10 centers in Switzerland and Lichtenstein.
Populations	185 participants; mean age 49 year-old. Inclusion criteria: inpatients and outpatients; adults with acute diarrhea (≥3 watery or loose stools in last 24 h). Exclusion criteria: diarrhea <3 d; blood in feces; fecal leukocytes; temperature >39 °C; friable and hemorrhagic mucosa in rectosigmoid; history of chronic diarrhea; polyps; colon cancer; Crohn's disease; ulcerative colitis; malabsorption; use of antidiarrheals or antibiotics in past 7 d; severe diarrhea (dehydration with weight loss >10%); associated major diseases. Number completing study: 93/105 (88.6%) in probiotic group and 92/106 (86.8%) in control group.	76 participants; mean age 33 year-old. Inclusion criteria: adults with acute diarrhea. Exclusion criteria: not stated. Number completing study: 40/47 (85.1%) in probiotic group and 38/46 (82.6%) in placebo group.
Intervention	Enterococcus strain SF68 (bioflorin; 75×10^6 CFU thrice daily for ≥5 d)	Live enterococcus strain SF 68 (bioflorin; 75×10^6 CFU thrice daily for 7 d)
Comparison	Placebo	Placebo
Outcomes	Number of participants with diarrhea by day of treatment. Mean stool frequency by day of treatment. No adverse effects due to probiotic.	Number of cases cured by day of treatment. No adverse effects due to probiotic.
Notes	Not stated: study duration, participants' race, funding source.	Not stated: study duration; exclusion criteria; participants' race; cause, characteristics, and duration of diarrhea; definition of cases cured; funding source.

Discussion

Normal gastrointestinal microbiota is known to play an important role in the protection of the host against gastrointestinal tract diseases and during acute diarrhea, it is shown to undergo major changes that promote the overgrowth of pathogenic microorganisms.[10] Probiotics are potentially beneficial in an episode of infectious diarrhea by competing for available nutrients and binding sites with the enteric pathogens, acidifying the gut contents, generating a variety of protective chemicals, and stimulating specific and non-specific immune responses.[11]

Although there are some theoretical risks regarding the safety of probiotics, the use of probiotics is safe in healthy people, with rare cases of infections were found in those who had risk factors such as immune deficiency, short bowel, or using central venous catheters.[12]

In contrast to the abundance of studies of probiotics efficacy in pediatric subjects with acute diarrhea, studies in adult subjects are very limited and thus only a couple of papers were appraised. Buydens et al[8] conducted a randomized, double-blind placebo-controlled clinical trial involving 211 adults with acute diarrhea where the efficacy of enterococcus SF 68 strain, administered orally in a dose of 75×10^6 colony-forming units (CFU) three times a day for 5 days, was compared with placebo. The probiotics-treated group had a significantly reduced mean duration of diarrhea (1.69 days) compared to control group (2.81 days) and after 4 days of treatment, all of the subjects given probiotics no longer had diarrhea, whereas 15.22% of placebo-treated subjects still had diarrhea. No adverse effects were found in the treatment group.

Similarly, a randomized, double-blind placebo-controlled clinical trial by Wunderlich et al[9] assessing

123 patients with acute diarrhea demonstrated that enterococcus SF 68 given orally in a dose of 75xl0[6] colony-forming units (CFU) thrice daily for 7 days significantly improved the recovery from diarrhea compared to placebo, i.e. 87.18% of those given probiotics were cured of diarrhea after 4 days of treatment, while only 59.46% of untreated subjects were cured. Adverse effects of probiotics were not assessed.

Interestingly, in contrast to the studies appraised in this paper, Mitra et al[13] found that enterococcus SF 68 did not significantly reduce the stool output and mean duration of acute infectious diarrhea in adults compared to placebo, although they found that the probiotics were well-tolerated. It is speculated that this was due to the differences in study design, including the diarrhea was caused by the severe types of secretory diarrhea-producing *Vibrio cholerae* and enterotoxigenic *Escherichia coli*. The similar negativity of stool cultures between the two groups rendered the inability of the probiotics to inhibit the pathogens. This difference of result suggests that future studies should also include the etiology of the acute infectious diarrhea and the stool culture results.

The effects of probiotics are widely known to be strain-specific and thus results acquired from one probiotic cannot be extrapolated to other species, including closely related strains.[14] As such, the efficacy of enterococcus SF 68 shown in this study cannot represent the efficacy of probiotics in general, although many studies involving various probiotics in various settings have mostly yielded positive outcomes, suggesting that most probiotics exert some common and effective mechanisms against a plethora of gastrointestinal pathogens.[7]

Data regarding the treatment efficacy of various strain of probiotics in adults with acute diarrhea, is very limited. Margreiter et al[15] demonstrated that a combination of *Lactobacillus gasseri* and *Bifidobacterium longum* shortens the duration and decreases the severity of acute self-limiting diarrhea in adults.[16] The control group, was given *Enterococcus feacium*, not placebo. Sudha et al[17] proposed that *Bacillus clausii* strain UBBC 07 and *Saccharomyces boulardii* strain unique 28 in patients suffering from acute diarrhea reduced the mean duration of diarrhea, the frequency of defecation, the severity of abdominal pain, and improved stool consistency compared to placebo, with no significant adverse effect. Both studies, however, were still preliminary as no control group was present. More studies with various strain is necessary to investigate the efficacy of probiotics in adults with acute infectious diarrhea.

The existing clinical trials also had a substantial limitation where the definition of diarrheal episodes varies and this may lead to misclassification and difficulty in comparing the outcomes.[18] Future research should standardize the definitions of acute diarrhea, treatment regimens, inclusion criteria, and outcome measures to allow good comparison of results across studies. Indeed, host and environmental factors, including age, diet and eating practices, level of sanitation, and exposure to antibiotics, may determine the commensal gut flora, and thus may alter probiotic efficacy.[19,20] Age, for instance, matters since there are differences in the diversity and maturation of microbiota composition in adults compared to children as found in the fecal samples and thus study results in children may not be applied to adults.[21] Since most cases of acute diarrhea are uncomplicated, self-limiting and need no specific treatment, cost-effectiveness analyses might be necessary, particularly for the patients in the developing countries.[7] Addressing all these issues would build a good foundation to create comprehensive evidence-based treatment guidelines.

Conclusion

Probiotics, specifically enterococcus SF 68, could improve the recovery and shorten the course of acute infectious diarrhea in adults, with no reported adverse effect (level of evidence 1b). Recommending the utilization of probiotics in adults with acute infectious diarrhea, however, should be proceeded with caution due to the limited availability and marked clinical variability of existing studies.

Acknowledgement

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