MEDwave

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
Medwave 2016; 16(Suppl5):e6801 doi: 10.5867/medwave.2016.6807

Are probiotics effective to prevent traveler's diarrhea?

Authors: Yazmín Pinos**[1,2]**, Victoria Castro-Gutiérrez**[2,3]**, Gabriel Rada**[1,2,4,5,6]**

Affiliation:
[1] Departamento de Medicina Interna, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[2] Proyecto Epistemonikos, Santiago, Chile
[3] Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[4] Programa de Salud Basada en Evidencia, Facultad de Medicina, Pontificia Universidad Católica de Chile
[5] GRADE working group
[6] The Cochrane Collaboration

E-mail: radagabriel@epistemonikos.org

Citation: Pinos Y, Castro-Gutiérrez V, Rada G. Are probiotics effective to prevent traveler's diarrhea?. *Medwave* 2016; 16(Suppl5):e6807 doi: 10.5867/medwave.2016.6807 **Publication date:** 23/12/2016

Abstract

Acute diarrhea is the most common disease that affects travelers, especially those visiting high-risk regions. Probiotics may prevent its occurrence, however the data supporting its use are not consistent and they are not recommended in current clinical guidelines. Searching in Epistemonikos database, which is maintained by screening multiple databases, we identified four systematic reviews including seven randomized trials addressing the question of this article. We extracted data, combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded probiotics might prevent traveler's diarrhea but the certainty of the evidence is low.

Problem

Acute diarrhea is the most common disease that affects travelers heading to at-risk areas. Although preventive measures related to hygiene have reduced the risk in many destinations, this is still high in some others [1].

The use of probiotics as prophylaxis for traveler's diarrhea seems attractive because of their beneficial effects over intestinal flora, and the reduction in colonization by pathogenic bacteria, in addition to their safety. However, data supporting their use are not consistent [2].

Methods

We used Epistemonikos database, which is maintained by screening multiple databases, to identify systematic reviews and their included primary studies. With this information, we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- Probiotics might prevent traveler's diarrhea but the certainty of the evidence is low.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found four systematic reviews [3],[4],[5],[6], that included seven randomized controlled trials [7],[8],[9],[10],[11],[12],[13].
What types of patients were included	Three studies only included adults [7],[11],[13]. One study included patients aged 10 to 80 years [10]. In three studies, the age range was not specified [8],[9],[12]. The included patients traveled to different destinations: From the United Kingdom to Belize [7] From Austria to Turkey/North Africa [8] From Denmark to Egypt [9] From Finland to Turkey [10] To warm climates [12] not specified From the United States to Mexico [13] One trial included several destinations [11]
What types of interventions were included	The trials used different probiotics and in different doses: • *Lactobacillus fermentum* 10^{11} CFU per day during three weeks or until the appearance of diarrhea [7]. • *Lactobacillus acidophilus* 10^{11} CFU per day during three weeks or until the appearance of diarrhea [7] (subgroup of study above). • *Saccharomyces boulardi* 5 X 10^9 and 2 X 10^{10} during three weeks [8]. • Combination of L. *acidophilus* + L. *bulgaricus* + *bifidobacterium bifidum* + *streptococcus thermophilus* 3 x 10^9 per two weeks [9]. • *Lactobacillus rhamnosus* GG 2 x 10^9 CFU per day during 1-2 weeks [10]. • *Lactobacillus rhamnosus* GG 20 x 10^9 CFU per day during 1-3 weeks [11]. • *Saccharomyces cereviciae* 2.5 x 10^9 or 5 x 10^9 and *Lactobacillus acidophilus* 2 x 10^8 or 2 x 10^9 during the travel (average 10 days for *Saccharomyces* and 12 days for *Lactobacillus*) [12]. • *Lactobacillus acidophilus* + *lactobacillus bulgaricus* 30 x 10^7 at 60 x 10^7 *lactobacilli* per tablet, four tablets in each meal for eight days and during 28 days [13]. All of the trials compared against placebo or standard treatment.
What types of outcomes were measured	The outcome was the development of diarrhea during the trip, defined as more than three stools per day for at least two days, or more than five stools in 48 hours.

Summary of findings

The information on the effects of probiotics to prevent traveler's diarrhea is based on seven randomized trials including 4,025 patients. All of the trials measured the outcome of diarrhea during the trip, defined as more than three stools per day for at least two days or more than five stools in 48 hours.

The summary of findings is as follows:

- Probiotics might prevent traveler’s diarrhea but the certainty of the evidence is low.

Probiotics to prevent traveler's diarrhea

Patients Travelers
Intervention Probiotics
Comparison Standard treatment

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUTH probiotics	**WITH probiotics**		
	Difference: patients per 1000			
Diarrhea	High risk destination**		RR 0.77 (0.60 to 1.00)	⨁⨁◯◯ [1,2] Low
	450 per 1000	347 per 1000		
	Difference: 103 patients less per 1000 (Margin of error: 0 to 180 less)			
	Intermediate risk destination**			
	150 per 1000	115 per 1000		
	Difference: 35 patients less per 1000 (Margin of error: 0 to 60 less)			
	Low risk destination**			
	50 per 1000	39 per 1000		
	Difference: 11 patients less per 1000 (Margin of error: 0 to 20 less)			

RR= Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITHOUT probiotics** is based on the risk in the control group of the trials. The risk **WITH probiotics** (and its margin of error) is calculated from relative effect (and its margin of error).

** Risk levels were obtained from a systematic review assessing the incidence at different destinations [1].

[1] The certainty of the evidence was reduced by one level for inconsistency (I^2 = 87%).
[2] The certainty of the evidence was reduced by one level for imprecision because the confidence interval includes the possibility of little or no effect.

About the certainty of the evidence (GRADE)*

⨁⨁⨁⨁
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⨁⨁⨁◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⨁⨁◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⨁◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- The evidence presented in this summary applies to people traveling to various destinations.
- Although the trials used different probiotics, the overall certainty of the existing evidence is low, so any conclusion regarding differences between different types of probiotics is not reliable.

About the outcomes included in this summary

- We only included the development of diarrhea as the critical outcome for decision-making, which in general agrees with the guidelines and reviews identified.

Balance between benefits and risks, and certainty of the evidence

- It is not possible to make an adequate balance between benefits and risks due to the existing uncertainty
- If the benefit were real, there would be important variation in this balance depending on different risk areas.

What would patients and their doctors think about this intervention

- Probiotics constitute a generally acceptable and well tolerated intervention by patients, although it is associated with costs.
- Patients and physicians putting more value on an uncertain benefit would probably be inclined to use this intervention. Those who place a higher value on the certainty of the evidence or costs would probably abstain from its use.
- In any case it is important to inform about the limitations of existing evidence.

Resource considerations

- The cost of probiotics could be an important factor in the decision, especially in situations where resources are limited.
- It is not possible to make an adequate cost / benefit balance due to the existing uncertainty.

Differences between this summary and other sources

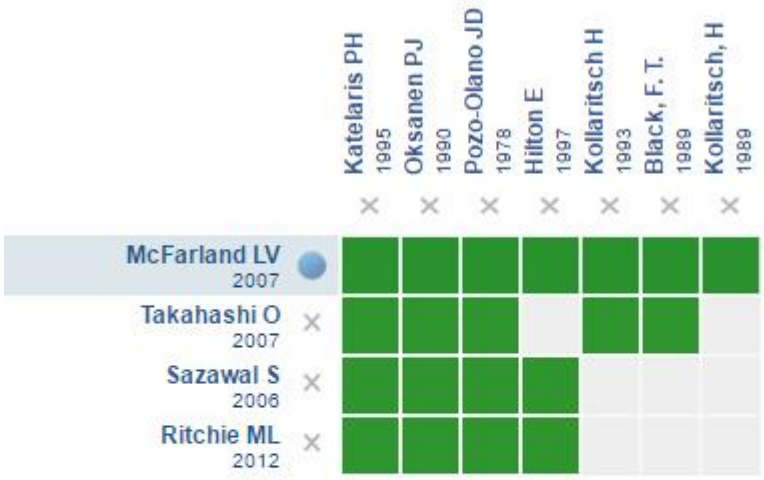
- The systematic reviews identified differ in their conclusions, so this summary partially agrees with them, especially in recognizing that the existing evidence is limited.
- The evidence presented in this summary is consistent with one of the main clinical guidelines, which makes a conditional recommendation against its use, based on evidence similar to what is discussed in this article [14].

Could this evidence change in the future?

- The probability that future evidence would change the conclusions of this article is very high, due to the existing uncertainty.
- None of the identified systematic reviews is sufficiently updated, so a new review could shed some additional light on this topic.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Probiotics for prevention of traveler's diarrhea

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

References

1. Steffen R, Hill DR, DuPont HL. Traveler's diarrhea: a clinical review. JAMA. 2015 Jan 6;313(1):71-80. | CrossRef | PubMed |
2. Riddle MS, DuPont HL, Connor BA. ACG Clinical Guideline: Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults. Am J Gastroenterol. 2016 May;111(5):602-22 | CrossRef | PubMed |
3. Sazawal S, Hiremath G, Dhingra U, Malik P, Deb S, Black RE. Efficacy of probiotics in prevention of acute

diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials. Lancet Infect Dis. 2006 Jun;6(6):374-82 | PubMed |
4. Ritchie ML, Romanuk TN. A meta-analysis of probiotic efficacy for gastrointestinal diseases. PLoS One. 2012;7(4):e34938 | CrossRef | PubMed |
5. McFarland LV. Meta-analysis of probiotics for the prevention of traveler's diarrhea. Travel Med Infect Dis. 2007 Mar;5(2):97-105 | PubMed |
6. Takahashi O, Noguchi Y, Omata F, Tokuda Y, Fukui T. Probiotics in the prevention of traveler's diarrhea: meta-analysis. J Clin Gastroenterol. 2007 Mar;41(3):336-7 | PubMed |
7. Katelaris PH, Salam I, Farthing MJ. Lactobacilli to prevent traveler's diarrhea? N Engl J Med. 1995 Nov 16;333(20):1360-1 | PubMed |
8. Kollaritsch H, Holst H, Grobara P, Wiedermann G. [Prevention of traveler's diarrhea with Saccharomyces boulardii. Results of a placebo controlled double-blind study]. Fortschr Med. 1993 Mar 30;111(9):152-6. | PubMed |
9. Black FT, Andersen PL, Ørskov J, Ørskov F, Gaarslev K, Laulund S, Steffen Robert, Lobel Hans, Haworth James, Bradley David J. Prophylactic Efficacy of Lactobacilli on Traveler's Diarrhea. Travel Medicine. 1989;:333-335 | CrossRef | Link |
10. : Oksanen PJ, Salminen S, Saxelin M, Hämäläinen P, Ihantola-Vormisto A, Muurasniemi-Isoviita L, Nikkari S, Oksanen T, Pörsti I, Salminen E, et al. Prevention of travellers' diarrhoea by Lactobacillus GG. Ann Med. 1990 Feb;22(1):53-6 | PubMed |
11. Hilton E, Kolakowski P, Singer C, Smith M. Efficacy of Lactobacillus GG as a Diarrheal Preventive in Travelers. J Travel Med. 1997 Mar 1;4(1):41-43 | PubMed |
12. Kollaritsch, H, Kremsner, PETER, Wiedermann, GERHARD, Scheiner, OTTO. Prevention of traveller's diarrhea: comparison of different non-antibiotic preparations. Travel Med Int. 1989;11:9-17 | Link |
13. de dios Pozo-Olano J, Warram JH Jr, Gómez RG, Cavazos MG. Effect of a lactobacilli preparation on traveler's diarrhea. A randomized, double blind clinical trial. Gastroenterology. 1978 May;74(5 Pt 1):829-30 | PubMed |
14. Riddle MS, DuPont HL, Connor BA. ACG Clinical Guideline: Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults. Am J Gastroenterol. 2016 May;111(5):602-22 | CrossRef | PubMed |

Author address:
[1] Facultad de Medicina
Pontificia Universidad Católica de Chile
Lira 63
Santiago Centro
Chile