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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Are probiotics effective in preventing urinary tract infection?

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Abstract

INTRODUCTION
Urinary tract infection is the most common bacterial infection and recurrences are common. Probiotics have been proposed as an alternative to decrease this risk. However, it is not clear if they are really effective.

METHODS
To answer this question we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

RESULTS AND CONCLUSIONS
We identified six systematic reviews including nine studies overall, of which seven were randomized trials. We concluded it is not clear whether probiotics decrease the risk of symptomatic urinary tract infection, because the certainty of the evidence is very low.

Problem

Urinary tract infection is the most frequent bacterial infection. It is associated to important morbidity, such as pyelonephritis, sepsis, abscess and renal failure. It is estimated that 40% of the adult population has presented at least 1 episode of urinary infection, of which 80 % are women. Approximately 20-30% of women with a first episode will experience a recurrence.

Probiotics have been proposed among the alternatives for prophylaxis. They would decrease the risk of urinary tract infection by creating a barrier against infectious pathogens, thus reducing the adherence, growing and colonization of such agents. However, the real efficacy of this intervention is not yet clear.

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) 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 when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- It is not clear whether probiotics reduce the risk of developing a symptomatic urinary tract infection because the certainty of the available evidence is very low.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found six systematic reviews [1],[2],[3],[4],[5],[6] that included nine primary studies [7],[8],[9],[10],[11],[12],[13],[14],[15], seven of which correspond to randomized controlled trials [7],[8],[9],[10],[11],[12], [13]. This table and the summary in general are based on the latter.
What types of patients were included*	All of the trials included women only. Two trials included patients with recurrent urinary tract infection [9],[11], four with an acute episode or with an episode of urinary tract infection within last year [7],[10],[12],[13] and one included healthy participants [8]. One trial included patients under 18 years [13] and the rest only included adults [7],[8],[9],[10],[11],[12]. Five trials excluded patients with use of prophylactic antibiotics [7],[9], [11],[12],[13], five excluded patients with concomitant disease [7],[9],[10],[11],[13] and three excluded pregnant women [7],[9],[11].
What types of interventions were included*	All of the trials used probiotics as intervention. Three trials used oral probiotics; Lactobacillus GG drink 4 x 108 CFU/100 ml 5 days a week for a year [12]; Lactobacillus GG drink 4 x 107 CFU/100 xml 5 times per month for 6 months [13]; Lactobacillus casei var rhamnosus GR-1 y Lactobacillus fermentum RC-14 1 x 109 CFU/100 ml 1 per day for 60 days [8]. The other four trials used probiotics in vaginal suppositories: Lactobacillus casei var rhamnosus GR-1 7.5 x 108 CFU by suppository twice a week for 26 weeks [9]; antibiotic treatment for 3 days with norfloxacin or cotrimoxazol, then lactobacillus casei var rhamnosus GR-1 plus Lactobacillus fermentum B-54 1.6 x 109 CFU by suppository twice a week during 2 weeks and at the end of the next 2 months [7]; Lactin-V 1 x 108 CFU by suppository 1 per day for 5 days [10]; Lactobacillus crispatus CTV-5 5x108 CFU once a day for 5 days [11].
What types of outcomes were measured	The outcomes, as they were grouped by the systematic reviews, were the following: symptomatic urinary tract infection episodes, total adverse effects, intervention withdrawal because of adverse effects and serious adverse effects.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of findings

The information about the effects of probiotics is based on six randomized trials [7],[9],[10],[11],[12],[13], that included 352 patients overall. The remaining trial did not report any of the outcomes of interest [8].

All of the trials reported episodes of symptomatic urinary tract infection, three reported total adverse effects [9],[10],[11] and one reported withdrawal due to adverse effects and serious adverse effects [10].

The summary of findings is the following:

- It is not clear whether probiotics decrease the risk of symptomatic urinary tract infection, because the certainty of the evidence is very low.
- Adverse effects of probiotics (abnormal vaginal discharge) are probably rare. The certainty of the evidence is moderate.

Probiotics for the prevention of urinary tract infection

Patients	Women with at least 1 episode of urinary tract infection
Intervention	Probiotics
Comparison	Placebo

Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT probiotics	WITH probiotics		
	Difference: patients per 1000			
Symptomatic urinary tract infection	395 per 1000	324 per 1000	RR 0.82 (0.6 to 1.12)	⊕◯◯◯[1,2,3] Very low
	Difference: 71 patients less (Margin of error: 158 less to 47 more)			
Adverse effects	The main adverse effect described was abnormal vaginal discharge, and to a lesser extent, vaginal itching and mild abdominal pain. The frequency of other adverse effects was low			⊕⊕⊕◯[4] Moderate

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
GRADE: Evidence grades of the GRADE Working Group (see later).

*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).

[1] The certainty of the evidence was downgraded in two levels because primary studies presented high risk of bias.
[2] The certainty of the evidence was downgraded in one level for imprecision, since decision-making would be different on both ends of the confidence interval.
[3] The certainty of the evidence was downgraded in one level for risk of publication bias.
[4] The certainty of the evidence was downgraded in one level because the primary studies presented high risk of bias, which would underestimate its magnitude.

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

- This evidence applies to women that have presented at least one episode of urinary tract infection.
- It should be noted that one trial included patients under 18 years, so the results could be extrapolated to this population.
- Even though we did not identify studies in men, or in people with comorbidities, in absence of direct evidence it is reasonable to extrapolate the conclusions of this summary to these groups.

About the outcomes included in this summary

- The outcomes included in the summary of findings table were those considered critical for decision-making by the authors of this article. In general, they coincide with those reported by the systematic reviews.
- We did not include the outcome recurrent urinary tract infection since the analysis of this variable was not different from the result for the outcome symptomatic urinary tract infection.

Balance between benefits and risks, and certainty of the evidence

- Even though it is an intervention with minimal adverse effects, it is not possible to adequately estimate the risk/benefit balance because of the uncertainty about the latter.

Resource considerations

- Commercial formulations of probiotics, such as those evaluated in the trials, are relatively expensive. It is not possible to estimate the cost/benefit balance because of the uncertainty about the latter.

What would patients and their doctors think about this intervention

- Faced with the evidence presented in this summary, most patients and clinicians should incline against the use of probiotics to prevent urinary tract infection.
- However, there is a currently a positive opinion about probiotics between many patients and also health professionals. This could lead people who put a higher value in an uncertain benefit, or a lesser value on adverse effects or cost, to use it. It is particularly important to inform these people about the uncertainty of the existing evidence.

Differences between this summary and other sources

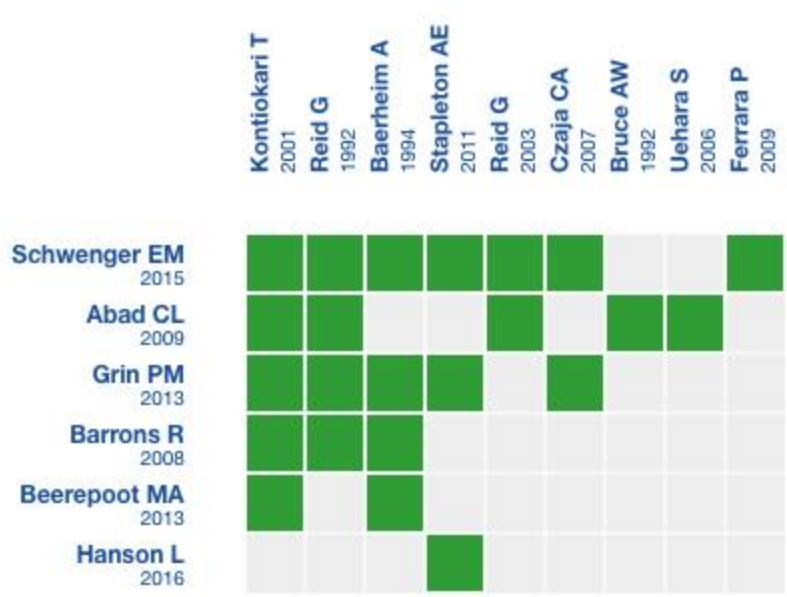
- The conclusions of this summary agree with most systematic reviews analysed.
- The main clinical guidelines, such as National Collaborating Centre for Chronic Conditions (NICE) [14] do not include probiotics as a therapeutic alternative for the prevention of urinary tract infections.

Could this evidence change in the future?

- The probability that future evidence modifies the conclusions of this summary is high, due to the existing uncertainty about the benefits.
- At least six ongoing trials were identified [15],[16],[17],[18],[19],[20] in the International Clinical Trials Registry Platform of the World Health Organization.
- New systematic reviews including a larger number of trials could contribute with shed more lights on this topic. We identified one ongoing systematic review [21] in PROSPERO database.

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.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Probiotics against placebo or no treatment for the prevention of urinary tract infection

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.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE 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).

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

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