**Critically Appraised Topic Alena Rakhman**

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| **Brief description of patient problem/setting** 29-year-old female w/ no PMHx presents to an urgent care c/o dysuria x 2 days. Pt states that she was diagnosed w/ a UTI 2 months ago, for which she finished a course of prescribed abx. She would like to know if there is anything she can do, in order to prevent the recurrence of UTIs in the future.  |

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| **Search Question:** What is the efficacy and safety of using probiotics as prophylaxis to prevent recurrent urinary tract infections in adult women? |

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| **Question Type:** [ ] Prevalence [ ] Screening [ ] Diagnosis[ ] Prognosis [x] Treatment [ ] Harms |

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| Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)? - RCTs can offer great supporting evidence as they are carefully planned experiments, reduce the potential for bias, and allow for comparison between intervention and control groups. - Retrospective cohort studies could also be utilized because they are below RCTs in terms of level of evidence in which study participants who receive a particular treatment can be followed over time and compared with another group of participants who did not receive the same treatment.  |

**PICO search terms:**

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| **P** | **I** | **C** | **O** |
| urinary tract infection | Lactobacillus | No probiotics | prophylactic efficacy |
| UTI | Lactobacilli |   | safety |
| cystitis | probiotics |  | incidence of adverse effects |
| recurrent UTI |  |  | recurrence  |
| adult women  |  |  |  |

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| **Search tools and strategy used:****Results found:****PubMed*** probiotics for urinary tract infection (best match) – 266
* probiotics for urinary tract infection (best match, 10 years) – 169
* probiotics for urinary tract infection (best match, 10 years, clinical trial, systematic reviews) – 13
* Lactobacillus for urinary tract infection (best match) – 287
* Lactobacillus for urinary tract infection (best match, 10 years, clinical trial, systematic reviews) – 25

**Cochrane Review** * probiotics for urinary tract infection (cochrane reviews) – 4
* probiotics for urinary tract infection (cochrane reviews, 2010-2019 – 4
* probiotics for urinary tract infection (trials) – 88
* probiotics for urinary tract infection (trials, 2010-2019) – 88

**Google Scholar*** probiotics for urinary tract infection (sort by relevance, any time) – 28,100
* probiotics for urinary tract infection (sort by relevance, 2010-2019) – 17,600
* probiotics for urinary tract infection “systematic review” (sort by relevance, 2010-2019) – 10,900
* Lactobacillus for urinary tract infection "systematic review" (sort by relevance, 2010-2019) – 12,100
* Lactobacillus for UTI "systematic review" (sort by relevance, 2010-2019) – 10,800

 Once I narrowed my search, it was not difficult to pick the articles since only few of them applied. I tried to find the most recent systematic reviews, and then moved on to RCTs. After reading the abstracts, I was able to decide which articles to include. |

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| **Citation:**1.Ng, Q. X., Peters, C., Venkatanarayanan, N., Goh, Y. Y., Ho, C. Y. X., & Yeo, W.-S. (2018). Use of Lactobacillus spp. to prevent recurrent urinary tract infections in females. Medical Hypotheses, 114, 49–54. https://doi.org/10.1016/j.mehy.2018.03.001 |
| **Type of article:** Systematic review and meta-analysis |
| **Abstract:** Urinary tract infections (UTIs) are the most common bacterial infections seen in the community, especially amongst females. The widespread use of antibiotics has led to the increased occurrence of E. coli resistant isolates worldwide. A promising non-antibiotic approach is the use of probiotic lactobacilli strains. This paper hypothesizes that Lactobacillus spp. containing products are able to prevent recurrent urinary tract infections in females. Using the keywords [lactobacillus OR lactobacilli OR probiotic] and [urinary tract infection OR UTI OR cystitis], a preliminary search on the PubMed, Ovid, Google Scholar and ClinicalTrials.gov database yielded 1,647 papers published in English between 1-Jan-1960 and 1-May-2017. 9 clinical trials with a total of 726 patients were reviewed. Different lactobacilli strains (in either oral or suppository formulation) were utilized and they demonstrated varying efficacy in the prevention of recurrent UTIs. Using a random-effects model, pooled risk ratio of at least one recurrent UTI episode during the entire study duration was 0.684 (95% CI 0.438 to 0.929, p < 0.001), per-protocol analysis. However, key limitations include significant inter-study variability and the limited duration of follow-up of most studies. Our hypothesis on the chemoprophylactic effects of probiotics for UTIs is plausible and supported by current data. Lactobacillus rhamnosus GR1 and Lactobacillus reuteri RC14 were the most commonly studied lactobacilli strains. Further and more robust randomized controlled trials with standardized lactobacilli strains and formulation are required for confirmation of effects.  |
| **Key points:*** Systematically reviewed 9 studies and pooled 6 studies randomizing a total of 620 patients.
* Products containing Lactobacillus spp. are able to prevent recurrent urinary tract infections in females is supported by current data.
* Intravaginal suppositories containing Lactobacillus crispatus CTV05, Lactobacillus rhamnosus GR1 and Lactobacillus reuteri RC14 are particularly effective against uropathogens and show the greatest efficacy for UTI prophylaxis.
* The safety, efficacy and cost-effectiveness of probiotics make them an ideal candidate for prophylactic use, whilst avoiding the long-term complications of sustained antibiotic treatment.
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| **Why I chose it:**I chose this article because it is the most recent systematic review that I was able to find, which directly focuses on my research question.  |
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| **Citation:**2.Stapleton, A. E., Au-Yeung, M., Hooton, T. M., Fredricks, D. N., Roberts, P. L., Czaja, C. A., … Stamm, W. E. (2011). Randomized, Placebo-Controlled Phase 2 Trial of a Lactobacillus crispatus Probiotic Given Intravaginally for Prevention of Recurrent Urinary Tract Infection. Clinical Infectious Diseases, 52(10), 1212–1217. https://doi.org/10.1093/cid/cir183 |
| **Type of article:** RCT |
| **Abstract:** ***Background:***Urinary tract infections (UTIs) are common among women and frequently recur. Depletion of vaginal lactobacilli is associated with UTI risk, which suggests that repletion may be beneficial. We conducted a double-blind placebo-controlled trial of a Lactobacillus crispatus intravaginal suppository probiotic (Lactin-V; Osel) for prevention of recurrent UTI in premenopausal women. ***Methods:***One hundred young women with a history of recurrent UTI received antimicrobials for acute UTI and then were randomized to receive either Lactin-V or placebo daily for 5 d, then once weekly for 10 weeks. Participants were followed up at 1 week and 10 weeks after intervention and for UTIs; urine samples for culture and vaginal swabs for real-time quantitative 16S ribosomal RNA gene polymerase chain reaction for L. crispatus were collected. ***Results:***Recurrent UTI occurred in 7/48 15% of women receiving Lactin-V compared with 13/48 27% of women receiving placebo (relative risk [RR], .5; 95% confidence interval, .2–1.2). High-level vaginal colonization with L. crispatus (>106 16S RNA gene copies per swab) throughout follow-up was associated with a significant reduction in recurrent UTI only for Lactin-V (RR for Lactin-V, .07; RR for placebo, 1.1; P , .01). ***Conclusions:***Lactin-V after treatment for cystitis is associated with a reduction in recurrent UTI. Larger efficacy trials of this novel preventive method for recurrent UTI are warranted.  |
| **Key points:*** Major goals of the study were to assess the ability of the probiotic to reduce the incidence of rUTI, to evaluate whether the probiotic achieved vaginal colonization, to assess effects on the vaginal microbiota of women after treatment for UTI, and to confirm the safety of the probiotic.
* The study found that Lactin-V reduced the risk of rUTI approximately as effectively as anti-microbial prophylaxis, achieved high-level vaginal colonization in most women, and was well tolerated.
* Premenopausal women aged 18–40 years with current, symptomatic, uncomplicated cystitis from the student health center at the University of Washington (Seattle, WA) from February 2006 through February 2009 were recruited.
* The total enrollment was 100 participants.
* Lactin-V treatment in women with rUTI resulted in robust and prolonged colonization with L. crispatus, with a trend of reducing the incidence of rUTI by approximately 50%.
* The protective effects of Lactin-V were even greater in those women who achieved the most robust colonization with L. crispatus and reflect an apparent treatment advantage for Lactin-V over natural recovery of the vaginal microbiota after an episode of rUTI.
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| **Why I chose it:**I chose this study because it is a randomized, double-blind, phase 2 trial that was performed in the United States. Additionally, according to the authors, “this study is novel in its application of a quantitative molecular method to assess vaginal microbiota following UTI, and thus to more precisely define sentinel changes in vaginal microbiota following standard treatment for UTI, either with or without a specific intervention designed to repopulate the vaginal bacterial biota, namely, the Lactin-V probiotic.” |
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| **Citation:**3.Grin, P. M., Kowalewska, P.M., Alhazzani, W., & Fox-Robichaud, A.E. (2013). Lactobacillus for preventing recurrent urinary tract infections in women: meta-analysis. Can J Urol, 20(1):6607-6614. |
| **Type of article:** Systematic review and meta-analysis  |
| **Abstract:** ***Introduction:*** Urinary tract infections (UTIs) are the most common infections affecting women, and often recur. Lactobacillus probiotics could potentially replace low dose, long term antibiotics as a safer prophylactic for recurrent UTI (rUTI). This systematic review and meta- analysis was performed to compile the results of existing randomized clinical trials (RCTs) to determine the efficacy of probiotic Lactobacillus species in preventing rUTI. ***Materials and methods:*** MEDLINE and EMBASE were searched from inception to July 2012 for RCTs using a Lactobacillus prophylactic against rUTI in premenopausal adult women. A random-effects model meta-analysis was performed using a pooled risk ratio, comparing incidence of rUTI in patients receiving Lactobacillus to control. ***Results:*** Data from 294 patients across five studies were included. There was no statistically significant difference in the risk for rUTI in patients receiving Lactobacillus versus controls, as indicated by the pooled risk ratio of 0.85 (95% confidence interval of 0.58-1.25, p = 0.41). A sensitivity analysis was performed, excluding studies using ineffective strains and studies testing for safety. Data from 127 patients in two studies were included. A statistically significant decrease in rUTI was found in patients given Lactobacillus, denoted by the pooled risk ratio of 0.51 (95% confidence interval 0.26-0.99, p = 0.05) with no statistical heterogeneity (I2 = 0%). ***Conclusion:*** Probiotic strains of Lactobacillus are safe and effective in preventing rUTI in adult women. However, more RCTs are required before a definitive recommendation can be made since the patient population contributing data to this meta-analysis was small.  |
| **Key points:*** Common risk factors for UTI in premenopausal women are different from those in other groups and include recent sexual intercourse, use of a diaphragm with spermicide or spermicidal condoms, a history of UTI, and recent antimicrobial use.
* The reviewed studies confirmed that Lactobacillus suppositories could be used safely, with some patients experiencing only mild side effects.
* These side effects can be attributed to the suppository vehicle of administration rather than Lactobacillus itself, since both control and experimental groups experienced a similar rate of side effects.
* The only study to administer Lactobacillus orally found that patients experienced no side effects.
* Oral administration may be a feasible solution to the occurrence of side effects and could result in better patient compliance.
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| **Why I chose it:**I chose this article because it was another systematic review that I was able to find, since there are not that many studies available on this topic.  |
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| **Citation:**4.Hanson, L., VandeVusse, L., Jermé, M., Abad, C. L., & Safdar, N. (2016). Probiotics for Treatment and Prevention of Urogenital Infections in Women: A Systematic Review. Journal of Midwifery & Women’s Health, 61(3), 339–355. https://doi.org/10.1111/jmwh.12472 |
| **Type of article:** Systematic review |
| **Abstract:** ***Introduction:*** Probiotics are a complementary and integrative therapy useful in the treatment and prevention of urogenital infections in women. This study extends the work of researchers who systematically investigated the scientific literature on probiotics to prevent or treat urogenital infections. ***Methods:*** A systematic review was conducted to determine the efficacy of probiotics for prevention and/or treatment of urogenital infections in adult women from January 1, 2008, through June 30, 2015. We searched in CINAHL, MEDLINE, Cochrane Central Register of Controlled Trials, Web of Science, Dissertations and Theses, and Alt-HealthWatch. After removing duplicates and studies that did not meet inclusion criteria, 20 studies were reviewed. All included at least one species of *Lactobacillus* probiotic as an intervention for treatment or prevention of urogenital infections. Data extracted included samples, settings, study designs, intervention types, reported outcomes, follow-up periods, and results. We evaluated all randomized controlled trials for risk of bias and made quality appraisals on all studies. ***Results:*** Fourteen of the studies focused on bacterial vaginosis (BV), 3 on urinary tract infections (UTIs), 2 on vulvovaginal candidiasis, and one on human papillomavirus (HPV) as identified on Papanicolaou test. Studies were heterogeneous in terms of design, intervention, and outcomes. Four studies were of good quality, 9 of fair, and 7 poor. Probiotic interventions were effective for treatment and prevention of BV, prevention of recurrences of candidiasis and UTIs, and clearing HPV lesions. No study reported significant adverse events related to the probiotic intervention. ***Discussion:*** The quality of the studies in this systematic review varied. Although clinical practice recommendations were limited by the strength of evidence, probiotic interventions were effective in treatment and prevention of urogenital infections as alternatives or co-treatments. More good quality research is needed to strengthen the body of evidence needed for application by clinicians.  |
| **Key points:*** Probiotic lactobacilli are commonly used choices for treating and preventing urogynecologic infections.
* Although clinical practice recommendations were limited by the strength of evidence, probiotic interventions appear to be effective in treatment and prevention of urogenital infections as an alternative or co-treatment.
* None of the probiotic interventions were associated with serious adverse events.
* More well-designed clinical research studies are needed on probiotics used to treat or prevent urogenital infections in women.
* If used as co-treatments, other evidence suggests that antibiotic and probiotic interventions should be separated by at least 2 to 4 hours to avoid the destruction of the live microorganisms in the gastrointestinal tract.
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| **Why I chose it:**I chose this article because it is a recent systematic review, and even though it looks at urogenital infections as a whole, 3 studies in particular were based on UTIs.  |
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| **Citation:**5.Schwenger, E. M., Tejani, A. M., & Loewen, P. S. (2015). Probiotics for preventing urinary tract infections in adults and children. Cochrane Database of Systematic Reviews. https://doi.org/10.1002/14651858.cd008772.pub2 |
| **Type of article:** Systematic review |
| **Abstract:** ***Background:*** Urinary tract infection (UTI) is a common bacterial infection that can lead to significant morbidity including stricture, abscess formation, fistula, bacteraemia, sepsis, pyelonephritis and kidney dysfunction. Mortality rates are reported to be as high as 1% in men and 3% in women due to development of pyelonephritis. Because probiotic therapy is readily available without a prescription, a review of their efficacy in the prevention of UTI may aid consumers in making informed decisions about potential prophylactic therapy. Institutions and caregivers also need evidence-based synopses of current evidence to make informed patient care decisions. ***Objectives:*** Compared to placebo or no therapy, did probiotics (any formulation) provide a therapeutic advantage in terms of morbidity and mortality, when used to prevent UTI in susceptible patient populations? Compared to other prophylactic interventions, including drug and non-drug measures (e.g. continuous antibiotic prophylaxis, topical oestrogen, cranberry juice), did probiotics (any formulation) provide a therapeutic advantage in terms of morbidity and mortality when used to prevent UTIs in susceptible patient populations? ***Search methods:*** We searched the Cochrane Kidney and Transplant Specialised Register to 21 September 2015 through contact with the Trials’ Search Co-ordinator using search terms relevant to this review. ***Selection criteria:*** Randomised controlled trials (RCTs) of susceptible patients (e.g. past history of UTI) or healthy people in which any strain, formulation, dose or frequency of probiotic was compared to placebo or active comparators were included. ***Data collection and analysis:*** All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at comparing probiotics to no therapy, placebo, or other prophylactic interventions were included. Summary estimates of effect were obtained using a random-effects model, and results were expressed as risk ratios (RR) and their 95% confidence intervals (CI) for dichotomous outcomes. ***Main results:*** We included nine studies that involved 735 people in this review. Four studies compared probiotic with placebo, two compared probiotic with no treatment, two compared probiotics with antibiotics in patients with UTI, and one study compared probiotic with placebo in healthy women. All studies aimed to measure differences in rates of recurrent UTI. Our risk of bias assessment found that most studies had small sample sizes and reported insufficient methodological detail to enable robust assessment. Overall, there was a high risk of bias in the included studies which lead to inability to draw firm conclusions and suggesting that any reported treatment effects may be misleading or represent overestimates. We found no significant reduction in the risk of recurrent symptomatic bacterial UTI between patients treated with probiotics and placebo (6 studies, 352 participants: RR 0.82, 95% CI 0.60 to 1.12; I2 = 23%) with wide confidence intervals, and statistical heterogeneity was low. No significant reduction in the risk of recurrent symptomatic bacterial UTI was found between probiotic and antibiotic treated patients (1 study, 223 participants: RR 1.12, 95% CI 0.95 to 1.33). The most commonly reported adverse effects were diarrhoea, nausea, vomiting, constipation and vaginal symptoms. None of the included studies reported numbers of participants with at least one asymptomatic bacterial UTI, all-cause mortality or those with at least one confirmed case of bacteraemia or fungaemia. Two studies reported study withdrawal due to adverse events and the number of participants who experienced at least one adverse event. One study reported withdrawal occurred in six probiotic participants (5.2%), 15 antibiotic participants (12.2%), while the second study noted one placebo group participant discontinued treatment due to an adverse event. ***Authors’ conclusions:*** No significant benefit was demonstrated for probiotics compared with placebo or no treatment, but a benefit cannot be ruled out as the data were few, and derived from small studies with poor methodological reporting. There was limited information on harm and mortality with probiotics and no evidence on the impact of probiotics on serious adverse events. Current evidence cannot rule out a reduction or increase in recurrent UTI in women with recurrent UTI who use prophylactic probiotics. There was insufficient evidence from one RCT to comment on the effect of probiotics versus antibiotics.  |
| **Key points:*** Nine studies were included involving a total of 735 participants.
* No significant difference in risk of recurrent UTI was seen for probiotics in comparison to placebo or antibiotic prophylaxis in either women or children.
* There was no significant difference found between probiotics and either placebo or antibiotic prophylaxis for harms.
* Adverse events, when reported, were poorly described with insufficient data to perform statistical evaluation.
* Overall the frequency of reported side effects was low and mild in nature.
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| **Why I chose it:**I chose this article because it is a Cochrane systematic review, providing the highest level of evidence, which I decided to include even though children were also included.  |
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**Summary of the Evidence:**

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| **Author (Date)** | **Level of Evidence** | **Sample/Setting (# of subjects/studies, cohort definition etc.)** | **Outcomes(s) studied** | **Key Findings** | **Limitations and Biases** |
| 1. Ng, Q. X., Peters, C., Venkatanarayanan, N., Goh, Y. Y., Ho, C. Y. X., & Yeo, W.-S. (2018). | Systematic review and meta-analysis | - preliminary search on the PubMed, Ovid, Google Scholar and ClinicalTrials.gov database yielded 1647 papers published in English between 01/01/1960 and 05/01/2017. - the inclusion criteria for this review were: (1) published clinical trial, (2) specified dose of probiotic was administered as an active intervention, (3) female subjects with clearly defined recurrent UTIs. - 9 studies were systematically reviewed, 6 studies were pooled and included in the meta-analysis, randomizing a total of 620 patients to either Lactobacillus prophylaxis or placebo/control. | - the primary outcome measures of interest were prophylactic efficacy and safety/incidence of adverse effects.  | - by using random-effects meta-analysis, the pooled risk ratio (RR) based on 6 RCTs with a total of 620 patients was 0.684 (95% CI 0.438 to 0.929, p < 0.001), supporting a beneficial prophylactic effect of lactobacilli products for UTI. - current data supports the hypothesis that products containing Lactobacillus spp. are able to prevent recurrent urinary tract infections in females. - intravaginal suppositories containing Lactobacillus crispatus CTV05, Lactobacillus rhamnosus GR1 and Lactobacillus reuteri RC14 are particularly effective against uropathogens and show the greatest efficacy for UTI prophylaxis. - probiotic suppositories are well-tolerated with no major side effects and avoid the growing issue of antibiotic resistance. - the safety, efficacy and cost-effectiveness of probiotics make them an ideal candidate for prophylactic use, whilst avoiding the long-term complications of sustained antibiotic treatment. | - only 9 studies were included in the systematic review and 6 in the meta-analysis.- only 4 studies were conducted in the US.- studies included both pre and post-menopausal women. - there is an increased risk of bias due to inter-study variations such as probiotic formulations, treatment dose, dosage routes (oral vs vaginal), and duration of treatment.  |
| 2. Stapleton, A. E., Au-Yeung, M., Hooton, T. M., Fredricks, D. N., Roberts, P. L., Czaja, C. A., … Stamm, W. E. (2011). | RCT, double-blind, phase 2  | - premenopausal women aged 18–40 years with current, symptomatic, uncomplicated cystitis were recruited from the student health center at the University of Washington (Seattle, WA) from February 2006 through February 2009. - eligible participants had a history of at least 1 prior symptomatic UTI treated within the past 12 months prior to the current UTI. - target sample size and final enrollment was 100 participants, 50 in each group.  | - major goals of the study were to assess the ability of the probiotic to reduce the incidence of recurrent UTI, to evaluate whether the probiotic achieved vaginal colonization, to assess effects on the vaginal microbiota of women after treatment for UTI, and to confirm the safety of the probiotic. - primary objective was to evaluate Lactin-V in healthy premenopausal women with recurrent UTI for the ability of the probiotic to reduce the incidence of cystitis and produce high-level vaginal colonization with L. crispatus at the end of 10 weeks.- secondary objectives were to evaluate patterns of vaginal colonization with L. crispatus in the vaginal microbiota and to confirm the safety of the probiotic.  | - Lactin-V reduced the risk of recurrent UTI approximately as effectively as anti-microbial prophylaxis, achieved high-level vaginal colonization in most women, and was well tolerated. - recurrent UTI occurred in 7/48 15% of women receiving Lactin-V compared with 13/48 27% of women receiving placebo (relative risk [RR], .5; 95% confidence interval, .2–1.2). - high-level vaginal colonization with L. crispatus throughout follow-up was associated with a significant reduction in recurrent UTI only for Lactin-V (RR for Lactin-V, .07; RR for placebo, 1.1; P, .01). - adverse effects were reported by 56% of participants who received Lactin-V and by 50% of participants who received placebo; the most common adverse effects included vaginal discharge or itching or moderate abdominal discomfort. - Lactin-V, an intravaginal probiotic composed of L. crispatus CTV-05, may reduce the rate of recurrent UTI in UTI-prone women by about one-half.  | - since this is an RCT, it provides lower evidence of evidence compared to systematic review/meta-analysis. - participants self-administered vaginal suppositories allowing for non-compliance bias.- sample size included only pre-menopausal women. - participants who developed UTI during study follow-up were treated and then they continued on with the study and were included in the final data. |
| 3. Grin, P. M., Kowalewska, P.M., Alhazzani, W., & Fox-Robichaud, A.E. (2013). | Systematic review and meta-analysis | - MEDLINE and EMBASE databases were searched from inception to 07/2012 for RCTs using a Lactobacillus prophylactic against recurrent UTI in premenopausal adult women. - data from 294 patients across five studies were included. - sensitivity analysis was performed (excluding studies using ineffective strains and studies testing for safety) resulting in inclusion of 2 studies with 127 patients.  | - the primary outcome for this meta-analysis was the incidence of at least one recurrent UTI. - the secondary outcome was adverse events, analyzed qualitatively.  | - there was no statistically significant difference in the risk for recurrent UTI in patients receiving Lactobacillus versus controls, as indicated by the pooled risk ratio of 0.85 (95% confidence interval of 0.58-1.25, p = 0.41). - a sensitivity analysis, which included patients from two RCTs (that used probiotic strains of Lactobacillus shown to colonize the vaginal epithelium), showed that probiotic Lactobacillus strains were associated with a significant reduction in the risk of recurrent UTI (RR 0.51; 95% CI 0.26-0.99, p = 0.05, I2 = 0%) when compared with control.- suppositories containing L. crispatus CTV-05 or a combination of L. rhamnosus GR-1 and L. fermentum B-54 are most effective.  | - studies with strains that did not achieve vaginal colonization were removed due to assumption that it could have skewed the data since those strains were seen as ineffective and are not probiotics. - only pre-menopausal women were included in the analysis.- suggested that side effects experienced by the participants are attributed to the suppository vehicle of administration rather than Lactobacillus itself, which could skew the views of the readers. - included a small sample size (294), which became even smaller after sensitivity analysis (127). - increased risk of bias due to inter-study variations, especially in regard to study duration ranging from 4 weeks to 12 months, and those included in the sensitivity analysis being 10 weeks and 12 months long.  |
| 4. Hanson, L., VandeVusse, L., Jermé, M., Abad, C. L., & Safdar, N. (2016). | Systematic review  | - CINAHL, MEDLINE, Cochrane Central Register of Controlled Trials, Web of Science, Dissertations and Theses, and Alt-HealthWatch databases were searched from 01/01/2008 through 06/30/2015. - after duplicates and studies that did not meet inclusion criteria were removed, 20 studies were reviewed, which included 14 randomized controlled trials (RCTs), one quasi-experiment, 2 prospective cohort studies, and 3 single-group investigations. - 14 of the studies focused on bacterial vaginosis (BV), 3 on vulvovaginal candidiasis, 2 on urinary tract infections (UTIs), and one on human papillomavirus (HPV) as identified on Papanicolaou test.  | - the study focused on probiotic interventions as treatment and/or prevention of select urogenital infections in women such as BV, candidiasis, UTI, and HPV. - the findings from the reviewed studies were analyzed by using a) quality assessment; b) study characteristics; c) definitions of urogenital infections; d) participant recruitment, inclusion, exclusion, and study restrictions; e) description of study interventions; f) outcomes by urogenital infection type; and g) adverse events.  | - probiotic interventions were effective for treatment and prevention of urogenital infections (BV, candidiasis, UTIs, HPV lesions) as alternatives or co-treatments.- no study reported significant adverse events related to the probiotic intervention. - 2 double-blind placebo controlled RCTs of probiotics to prevent UTI recurrences were examined for commonalities and differences. - first RCT study demonstrated that the probiotic intervention significantly increased colonization with *L crispatus* and this led to a reduction in UTI recurrence.- second RCT found that the probiotic intervention did not meet the noninferiority margin, but among women with uncomplicated UTI, the average number of UTI recurrences was significantly less in the probiotic group compared to controls.- second RCT also showed that antibiotic resistance increased in the control group but not in the probiotic group participants. | - the study included a typo, reporting a total of 3 studies on UTI and 2 on candidiasis in the abstract, but actually including 3 studied on candidiasis and 2 on UTI. - only 2 studies were associated with recurrent UTI, which provided a small sample size. - statistical analysis was not performed because studies were heterogeneous in terms of design, intervention, and outcomes, including those reporting on the same infection. - there were significant variations among the probiotic interventions, such as strain, species, dosage, frequency, routes ofadministration, and treatment duration.- the rationale for dosing and/or the treatment duration were not provided in the studies. - a detailed quality assessment was made of each study due to lack of statistical analysis, rating the 2 studies on UTI as moderate, with RCT being of good quality. - tracking of primary and even secondary outcomes compared to study aims was confounded by a lack of precision and clarity in a number of the studies reviewed. - only 6 of the RCTs reviewed had low risk of bias as assessed by Cochrane Collaboration Risk of Bias of Randomized Controlled Trials Assessment.  |
| 5. Schwenger, E. M., Tejani, A. M., & Loewen, P. S. (2015). | Systematic review | - Cochrane Kidney and Transplant Specialised Register were searched up to 09/21/2015 through contact with the trials’ search coordinator. - RCTs of susceptible patients or healthy people in which any strain, formulation, dose or frequency of probiotic was compared to placebo or active comparators were included. - 9 studies that involved 735 people were included (4 studies compared probiotic with placebo, 2 compared probiotic with no treatment, 2 compared probiotics with antibiotics in patients with UTI, and 1 study compared probiotic with placebo in healthy women).- 7 studies involved women or girls with recurrent UTIs, 1 looked at children with abnormal urinary tracts, and 1 investigated UTI in healthy women.  | - whether probiotics (any formulation) provide a therapeutic advantage in terms of morbidity and mortality, when used to prevent UTI in susceptible patient populations when compared to:(1) placebo or no therapy.(2) other prophylactic interventions, including drug and non-drug measures (e.g. continuous antibiotic prophylaxis, topical oestrogen, cranberry juice). | - there was no significant reduction in the risk of recurrent symptomatic bacterial UTI between patients treated with probiotics and placebo (6 studies, 352 participants: RR 0.82, 95% CI 0.60 to 1.12; I2 = 23%) with wide confidence intervals, and statistical heterogeneity was low. - there was no significant reduction in the risk of recurrent symptomatic bacterial UTI was found between probiotic and antibiotic treated patients (1 study, 223 participants: RR 1.12, 95% CI 0.95 to 1.33). - the most commonly reported adverse effects were diarrhea, nausea, vomiting, constipation and vaginal symptoms.  | - most studies had small sample sizes and reported insufficient methodological detail to enable robust assessment. - there was a high risk of bias in the included studies which lead to inability to draw firm conclusions and could mean that any reported treatment effects may be misleading or represent overestimates. - studies included different patient populations resulting in the analysis of separate small groups of studies instead of the evidence base as a whole.- there were many different species of probiotics used, different dosage forms such as vaginal and oral, and probiotics were given for varying lengths of time. - if authors of the study did not respond to missing data requests, the worst outcome was assigned for all missing data points in the experimental treatment group. - there was some reporting bias in that several studies did not report on symptomatic bacterial UTI and reported limited information on harm. - adequate allocation concealment was described in 4/8 included studies, and only 2 studies were double blinded.  |

**Conclusions(s):**

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| 1. Ng, Q. X., Peters, C., Venkatanarayanan, N., Goh, Y. Y., Ho, C. Y. X., & Yeo, W.-S. (2018). | - products containing Lactobacillus spp. are able to prevent recurrent urinary tract infections in females.- intravaginal suppositories containing Lactobacillus crispatus CTV05, Lactobacillus rhamnosus GR1 and Lactobacillus reuteri RC14 are particularly effective against uropathogens and show the greatest efficacy for UTI prophylaxis. - probiotic suppositories are well-tolerated with no major side effects and avoid the growing issue of antibiotic resistance. - the safety, efficacy and cost-effectiveness of probiotics make them an ideal candidate for prophylactic use, whilst avoiding the long-term complications of sustained antibiotic treatment. |
| 2. Stapleton, A. E., Au-Yeung, M., Hooton, T. M., Fredricks, D. N., Roberts, P. L., Czaja, C. A., … Stamm, W. E. (2011). | - Lactin-V reduced the risk of rUTI approximately as effectively as anti-microbial prophylaxis, achieved high-level vaginal colonization in most women (with a trend of reducing the incidence of rUTI by 50%) and was well tolerated. - protective effects of Lactin-V were even greater in those women who achieved the most robust colonization with L. crispatus which could mean an apparent treatment advantage for Lactin-V over natural recovery of the vaginal microbiota after an episode of rUTI.- adverse effects were reported by 56% of participants who received Lactin-V and by 50% of participants who received placebo, with the most common adverse effects being vaginal discharge or itching or moderate abdominal discomfort.  |
| 3. Grin, P. M., Kowalewska, P.M., Alhazzani, W., & Fox-Robichaud, A.E. (2013). | - there was no statistically significant difference in the risk for recurrent UTI in patients receiving Lactobacillus versus controls. - a sensitivity analysis, which included patients from two RCTs (that used probiotic strains of Lactobacillus shown to colonize the vaginal epithelium), showed that probiotic Lactobacillus strains were associated with a significant reduction in the risk of recurrent UTI when compared with control.- suppositories containing L. crispatus CTV-05 or a combination of L. rhamnosus GR-1 and L. fermentum B-54 are most effective. |
| 4. Hanson, L., VandeVusse, L., Jermé, M., Abad, C. L., & Safdar, N. (2016). | - probiotic interventions were effective for treatment and prevention of urogenital infections (BV, candidiasis, UTIs, HPV lesions) as alternatives or co-treatments.- no study reported significant adverse events related to the probiotic intervention. - 2 double-blind placebo controlled RCTs of probiotics to prevent UTI recurrences were examined for commonalities and differences: (1) probiotic intervention significantly increased colonization with *L crispatus* and this led to a reduction in UTI recurrence.(2) probiotic intervention did not meet the noninferiority margin, but among women with uncomplicated UTI, the average number of UTI recurrences was significantly less in the probiotic group compared to controls; antibiotic resistance increased in the control group but not in the probiotic group participants. |
| 5. Schwenger, E. M., Tejani, A. M., & Loewen, P. S. (2015). | - no significant difference in risk of recurrent UTI was seen for probiotics in comparison to placebo or antibiotic prophylaxis in either women or children. - there was no significant difference found between probiotics and either placebo or antibiotic prophylaxis for harms. - adverse events, when reported, were poorly described with insufficient data to perform statistical evaluation. |
| The overall conclusion is that there is evidence that probiotics, when used as prophylaxis to prevent recurrent urinary tract infections in adult women, are effective with almost no side effects, but more studies need to be performed before there could be a change in clinical guidelines.  |

**Clinical Bottom Line:**

What is the efficacy and safety of using probiotics as prophylaxis to prevent recurrent urinary tract infections in adult women?

In recurrent UTIs, there is disruption of normal vaginal flora, which can predispose patients to chronic intermittent urogenital infections. The role of probiotic prophylaxis is to restore and maintain a healthy host microbiome. One of the most common side effects associated with long term antibiotic use in women is yeast vaginitis. Additionally, antibiotics resistance among uropathogens has been shown to increase with long term use. Several indigenous species of lactobacilli can be found in the vaginal flora of healthy women, acting as a protectant against pathogenic colonization. By using probiotics as a prophylaxis, the costs and morbidity associated with UTIs can be reduced, including time lost from work, healthcare costs, antimicrobial use as well as the development of antimicrobial resistance.

Probiotics can restore normal vaginal flora and exert a protective effect against UTIs by releasing antimicrobial substances such as lactic acid, out-compering pathogenic bacteria like E. Coli, preventing the adhesion of pathogens to epithelial cells, as well as the non-specific activation of the innate immune system.

Classifying the weight of the evidence toward my clinical bottom line, article 1 provided with the highest level of evidence, followed by article 2, 5 3, and lastly 4. Article 1 is a systematic review with meta-analysis, was the most recently published, and included the greatest amount of studies that pertained to my research question. Article 2 also provided with high level of evidence even though it is an RCT, because it is a double-blind phase 2 study, and was heavily credited as a model study by the included systematic reviews and meta-analysis. Article 5 is a Cochrane systematic review, which is a trusted source of information, but did not include many studies in its analysis, and when it came to the conclusion, did not find a significant difference due to insufficient data. Article 3 was also a systematic review with meta-analysis which answered my question, but one of the main limitations was its small sample size. Lastly, article 4 looked at other urogenital infections and only 2 RCTs pertained to UTI.

According to the articles that I have included, the clinical bottom line is that probiotic strains of Lactobacillus are safe and effective in preventing recurrent UTIs in adult women. Probiotic prophylaxis did not result in significant side effects, can potentially aid when it comes to antibiotic resistance, lower socioeconomic costs associated with recurrent UTI, and eliminate side effects of long-term antibiotic use such as yeast vaginitis. However, since there are few studies available on the subject, clinical guidelines cannot be made at this time. Additionally, there are also many inter-study variations, such as probiotic formulations (especially different strains), treatment dose, dosage routes between oral and vaginal (as oral could mean better compliance), and the duration of treatment. More RCTs should be performed on the topic with the aim of standardizing the treatment with longer follow-ups.