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REVIEW

The Role of *Lactobacillus* Probiotics in the Treatment or Prevention of Urogenital Infections – A Systematic Review

C.L. ABAD – N. SAFDAR

Section of Infectious Diseases, Department of Medicine, University of Wisconsin Medical School, Madison, Wisconsin and the University of Wisconsin Hospital and Clinics, Madison, WI, USA

Correspondence: Dr. Safdar at H4/574 University of Wisconsin Hospital and Clinics, Madison, WI 53792; ns2@medicine.wisc.edu

Summary

Probiotics are increasingly being used to treat and prevent urogenital infections. However, a critical assessment of their efficacy in major urogenital infections is lacking. We report the results of a systematic review to determine the efficacy of probiotics for prevention or treatment of three major urogenital infections: bacterial vaginosis, vulvovaginal candidiasis, and urinary tract infection. Using multiple computerized databases, we extracted data from clinical trials using a lactobacillus-containing preparation to either prevent or treat a urogenital infection. Of 25 included studies, 18 studies used lactobacillus preparations for treatment or prevention of urogenital infections and seven studies focused solely on vaginal colonization. Four studies included patients with vaginal candidiasis, five included patients with urinary tract infections, and eight included patients with bacterial vaginosis. One included several types of genitourinary infections. Overall, lactobacilli were beneficial for the treatment of patients with bacterial vaginosis. No clear benefit was seen for candidiasis or urinary tract infection. Studies were heterogenous, with some limited by a small population size. In conclusion, the use of certain lactobacillus strains such as *L. rhamnosus* GR-1 and *L. reuteri* for prevention and treatment of recurrent urogenital infection is promising, especially for recurrent bacterial vaginosis. Scant data on the use of probiotics for urinary tract infection and vulvovaginal candidiasis precludes definitive recommendations. Further research and larger studies on types of lactobacilli strains, dosage of lactobacilli, optimal route and vehicle of administration are needed.

Key words: **Probiotic, lactobacillus, bacterial vaginosis, urinary infection.**

INTRODUCTION

Urogenital infections such as vulvovaginal candidiasis (VVC), bacterial vaginosis (BV) and urinary tract infections (UTI) affect billions of women each year, resulting in considerable morbidity and healthcare costs.[1-4] Options for prevention and treatment of these common conditions are limited, particularly for women with recurrent infections.[5-9]

The prevailing literature suggests that imbalance in the normal vaginal bacterial flora, comprising mainly lactobacilli, may contribute to the pathogenesis of urogenital infections, in particular, BV and UTI.[10] Restoration of the normal vaginal flora by the use of probiotics containing lactobacilli has been proposed as a novel approach for the prevention and treatment of urogenital infections.[11]

Probiotics are defined as living organisms administered to promote the health of the host by treating or preventing disease.[12] Based on the FAO/WHO working group definition, they are defined as "live microorganisms, which when administered in adequate amounts confer a health benefit on the host".[13] Several mechanisms of action have been proposed for the potential beneficial effect of a probiotic: contributing to intestinal microbial balance, inhibiting the growth of

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pathogenic bacteria, with the inhibition ascribed to metabolites such as fatty acids, hydrogen peroxide, ammonia, and bacteriocin.[14] Production of these substances by lactobacilli prevents colonization by harmful microorganisms either by reducing their number, or by affecting their metabolism.[15] Lactobacilli-containing probiotics have been studied for a number of intestinal and non-intestinal conditions, including antibiotic-associated diarrhea[16], *Clostridium difficile* infection,[17,18] inflammatory bowel disease,[19,20] irritable bowel syndrome and urogenital infections.[11] However, a systematic assessment of the evidence for a role of probiotics for the prevention and treatment of urogenital infections is lacking.

We undertook a systematic review to determine whether *Lactobacillus*-containing probiotics are beneficial in the treatment or prevention of three major urogenital syndromes: vulvovaginal candidiasis (VVC), urinary tract infection (UTI) and bacterial vaginosis (BV).

METHODS

Search strategy

We performed a comprehensive search of medical databases restricted to the adult population and the English language from inception to Dec 31, 2007 (PUBMED, CINAHL, EMBASE). The Cochrane collaboration, ACP and DARE databases were searched. Search terms included: lactobacillus or probiotic, combined with urinary tract infection, yeast vaginitis, vulvovaginal candidiasis, or bacterial vaginosis. Reference lists from all included studies were also manually reviewed. Search terms were also entered into Google Scholar to identify additional articles of possible relevance.

Inclusion criteria

We included all clinical trials that had a control group. This included randomized controlled trials and non-randomized trials that included populations given *Lactobacillus* versus no treatment or a comparator for treatment or prevention of genitourinary infections, including urinary tract infections, bacterial vaginosis, and yeast vaginitis. Studies that focused on colonization or restoration of normal vaginal flora were also included in the systematic review but analyzed separately because of the intermediate outcomes that they assessed.

Data extraction and validity assessment

Data were extracted independently and reviewed by both authors. We extracted data on setting, study design, type of intervention, outcomes reported, period of follow-up and results. Relative risk ratios were calculated for each study. We used the Cochrane Handbook on Systematic Reviews and the CONSORT and QUORUM statements for guidelines on reviewing studies and extracting data and conducting analyses.

Statistical analysis

The studies were heterogenous, and a formal meta-analysis was not appropriate. We summarized the results of the individual studies.

RESULTS

A total of 39 studies were identified that described *Lactobacillus* in the context of urogenital infections. Twenty-five of these met our inclusion criteria.[21-45] The remainder was excluded because they were undertaken in the pediatric population,[21,22] the use of *Lactobacillus* was not part of the intervention,[23-27] it was not an interventional study,[28-31] or data to calculate relative risk was not provided.[57-59] Details of the literature search leading to final selection are shown in *Figure 1*.

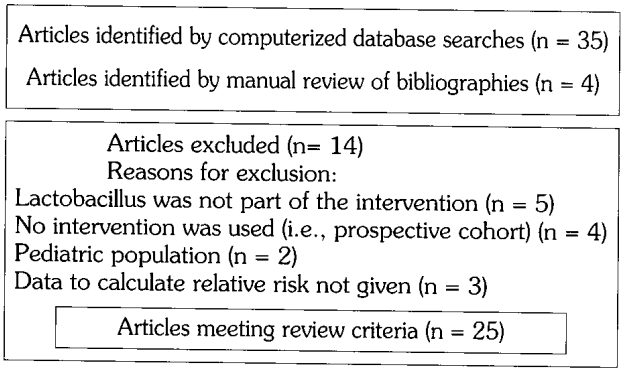

FIGURE 1 - Flowchart depicting literature search.

Study characteristics

The characteristics of the included studies, categorized according to type of infection, whether they were used for prevention, therapy, or for restoration of normal flora, are shown in *Tables 1-4*. The majority of studies were randomized controlled trials. [21-24,26,27,30-33,35,37-39,41,42,44] The remaining studies were before-after trials, using historical controls. [32-38] Four studies included VVC, [35,36,39,40] five UTI, [32,33,41-43] and eight BV.[21,22,25-27,31,32,45] One study included multiple types of urogenital infections.[44] The studies that focused exclusively on colonization by *Lactobacillus* or restoration of normal vaginal flora are shown in *Table 4*.[34,37,39,45-48]

All five studies on urinary infections focused on prevention, and all eight studies on BV focused on treatment. There were two trials on treatment of VVC [35,49] and two trials on prevention.[36,40] All studies were done in an outpatient setting, and the majority included healthy, pre-menopausal, non-pregnant women. However, one trial included the post-menopausal population,[46] and one study each focused on pregnant women,[50] and HIV patients,[49] respectively.

TABLE 1 - *Characteristics of studies on prevention and treatment of vaginal candidiasis.*

STUDY (First Author), Year (Ref)	**TYPE OF STUDY**	**PATIENTS, (n)**	**PATIENT DESCRIPTION**	**VEHICLE TYPE**	**STRAIN**	**LENGTH of TREATMENT**	**RR (95% CI) *p value***
Prevention							
Hilton,1992 [36]	Prospective, crossover trial	33	Pre-menopausal women with h/o chronic VVC	Oral	*L. acidophilus* yogurt, 10^8 CFU/ml	Daily for 6 months	0.39 (0.17-0.7) *p<0.009*
Pirotta, 2004 [40]	Randomized, double blind, placebo controlled, factorial 2x2 trial	235	Healthy non-pregnant women who recently finished a short course of antibiotics for a non-gynecologic infection	Oral and vaginal pessary	Oral: *L. rhamnosus, Bifidobacterium longum* Vaginal pessary: *L rhamnosus, L delbrueckii, L acidophilus*, and *Streptococcus thermophilus*	Daily for 4 days	Oral lactobacillus RR:1.09 (0.68-1.76) *P = 0.8* Vaginal lactobacillus RR1.38 (0.75-2.54) *P >0.05*
Treatment							
Hilton, 1995 [35]	Quasi-experimental trial	28	h/o recurrent VVC, >5x/year	Vaginal suppository	*L. rhamnosus GG*, 10^9/capsule	Twice daily for 7 days	0.201 (0.03-1.18) *P = 0.19*
Williams, 2001[49]	Randomized, double blind, placebo controlled trial	164	Young HIV patients, stratified according to CD4 counts	Intravaginal capsule	*L. acidophilus*	Weekly for 19 months	0.54 (0.26 - 1.10) *P = 0.14*

RR, relative risk; CI, confidence interval

TABLE 2 - *Characteristics of studies on prevention of urinary tract infections.*

STUDY (First Author), Year (Ref)	**TYPE OF STUDY**	**PATIENTS, (n)**	**PATIENT DESCRIPTION**	**VEHICLE TYPE**	**STRAIN**	**LENGTH of TREATMENT**	**RR (95% CI) *p value***
Reid 1992 [42]	Randomized, placebo-controlled trial	41	Pre-menopausal women, given lactobacillus after antibiotic therapy.	Intravaginal suppository	*L. casei var. rhamnosus* GR-1 *L. fermentum* B54 $1.6x10^9$ /capsule	Twice weekly for two weeks, then at the end of each of the next 2 mos.	0.45 (0.14-0.125) *P= 0.26*
Bruce, 1992 [32]	Quasi-experimental trial	10	Both pre and post-menopausal women, h/o recurrent UTI (>4x/12mos)	Intravaginal suppository	*L. casei* var. *rhamnosus* GR-1 *L. fermentum* B54 $>1.6x10^6$/capsule	Weekly for 12-16 mos.	0.64 (0.32-1.08) *P = 0.25*
Reid, 1995 [41]	Randomized, single blind trial	55	Healthy, pre-menopausal women, h/o >4 UTI/yr	Intravaginal suppository	*L. casei* v. *rhamnosus* GR-1, L. *fermentum* B54 $1x10^9$/vial	Weekly for 12 mos	RR = 0.42 (0.22-0.67) *P1 = 0.001* RR = 0.62 *P2 = < 0.05*
Kontokiari, 2001 [43]	Randomized, open-controlled trial	150	Healthy, pre-menopausal women	Oral	*Lactobacillus* GG $4x10^{10}$ CFU/ 100ml	5d/wk for 1yr	1.05 (0.63-1.76) *P = 0.5*
Uehara, 2006 [33]	Quasi-experimental trial	9	Healthy, young women, 2 episodes UTI/12 mos	Intravaginal suppository	*L. crispatus* GA 98322, $1x10^8$ CFU/capsule	Every 2 days for 1 year	1.28 (0.78-2.11) *P = 0.45*

RR, relative risk; CI, confidence interval

TABLE 3 - *Characteristics of studies on treatment of bacterial vaginosis, and mixed infections.*

STUDY (First Author), Year (Ref)	TYPE OF STUDY	PATIENTS, (n)	PATIENT DESCRIPTION	VEHICLE TYPE	STRAIN	LENGTH of TREATMENT	RR (95% CI) *p value*
Neri, 1993 [50]	Randomized placebo controlled trial	84	Young, healthy, pregnant women in the 1st trimester with BV (Amsel's criteria)	Vaginal douche	*L. acidophilus* 10^8 CFU/ml	Twice daily for 7 days	1 mo, RR 0.147 (0.05-0.39) *P <0.0001*
Parent, 1996 [53]	Multi-center, randomized, placebo controlled trial	32	Healthy, pre-menopausal, and (8 pregnant women with BV (Amsel's criteria)	Intravaginal suppository	*L. acidophilus* 10^7 CFU/ml and estriol	Once to twice daily for 6 days	14 d, RR 0.308 (0.1-0.76) *P = 0.02*
Hallen, 1991 [54]	Randomized, double-blind, placebo controlled trial	60	Healthy, pre-menopausal women with BV (Amsel's criteria)	Intravaginal suppository	*L. acidophilus* 10^8-10^9 CFU/tab	Twice daily for 6 days	At 7-10d, RR 0.43 (0.27-0.62) *P = 0.0001*
Drago, 2007 [38]	Quasi experimental trial	40	Pre- or post - menopausal women, non pregnant, with BV (Amsel's criteria)	Vaginal douche	*L. acidophilus*, 10^9 CFU/ml	Daily for 6 days	0.143 (0.04-0.39) *P = 0.0001*
Eriksson, 2005 [55]	Double-blind, placebo controlled trial	187	Healthy non-pregnant adults, with BV (Amsel's criteria); pt. were treated with vaginal clindamycin ovules prior to lactobacilli use	Intravaginal tampons	*L. gasseri, L. casei var rhamnosus, L. fermentum* 10^8 CFU/tampon	Weekly for 12 mos	0.94 (0.77-1.14) *P = 0.64*
Anukam, 2006 [58]	Randomized controlled trial	40	Healthy pre-menopausal black women with BV by Amsel's and Nugent's criteria and BV Blue test	Intravaginal suppository	*L. rhamnosus GR-1 and L. reuteri RC-14*, $1x10^9$/capsule	Nightly for 5 days	0.23 (0.07-0.6) *P = 0.003*
Anukam, 2006 [57]	Randomized, double blind trial	125	Healthy pre-menopausal black women with BV by Amsel's and Nugent's criteria and BV Blue test. Pretreated with oral Metronidazole x5-7d	Oral	*L. rhamnosus* GR-1 $1x10^9$/ capsule; *L. reuteri* RC-14 $1x10^9$/capsule	Twice daily for 30 days	0.03 (0.003 -0.3) *P = 0.0001*
Hillier, 2002 [59]	Randomized, double-blind, placebo controlled trial	424	Patients with BV as defined by Nugent's criteria; no other demographic given in abstract	Intravaginal capsule	*L. crispatus* CTV strain, 10^8/capsule	Twice daily for 3 days, every month, up to 3 months	At 30 days - 1.23 (0.98-1.55) *P = 0.08*
Shalev, 1996 [44]	Randomized, double blind trial	46	Pts with h/o recurrent BV (20) or VVC (18) or both (8).	Oral	*L. acidophilus* 10^8/mL	*Lactobacillus* daily, then none, then pasteurized yogurt at 2 mos. intervals	RR of VVC = 1.16 (0.55-2.54) *P1 = 0.94* RR of BV = 0.45 (0.18-1.03) *P2 = 0.12*

RR, relative risk; CI, confidence interval

TABLE 4 - *Studies that determined colonization or restoration of normal flora.*

STUDY (First Author), Year (Ref)	TYPE OF STUDY	PATIENTS, (n)	PATIENT DESCRIPTION	VEHICLE TYPE	STRAIN	LENGTH of TREATMENT	EFFECT ON VAGINAL FLORA
Reid, 2001 [39]	Randomized, double blind trial	42	Pre-menopausal, healthy women	Oral	Grp 1 L. *rhamnosus* GR1/ L. fermentum RC 14, $8x10^8$ Grp 2 GR1/ RC 14, $1.6x10^9$ Grp 3 GR1/ RC 14, $6x10^9$ Grp 4 L. *rhamnosus* GG (control) 10^{10}	Daily for 28 days	Grp 1-4: 6/10, 9/12 , 5/11, and 3/9, were colonized with lactobacilli at 28d. This was significant in Grp 2 (p = 0.017)
Cadieux, 2002 [45]	Randomized controlled trial	29	Healthy premenopausal, non pregnant women	Intravaginal capsule	*L. rhamnosus* GR-1 and *L. reuteri* RC-14, 10^9 / cap *L. rhamnosus* GG, 10^9 / cap	One dose	Higher levels of colonization with GR-1/RC-14 compared to GG at 2 weeks; 11/15 v 3/15. (p =0.009)
Reid, 2003 [47]	Randomized, double blind, placebo controlled trial	64	Healthy pre-menopausal women, with no h/o VVC in the past year	Oral	*L rhamnosus* GR, $x10^9$ *L. reuteri* RC-14	Daily for 60 days	Restoration from BV to normal microflora in 37% compared to 13% (p =0.02)
Colodner, 2003 [46]	Randomized controlled trial	42	Post-menopausal women	Oral	*L. rhamnosus* GG, 10^9 CFU	Daily and twice daily for 30 days	Only 4/42 (9.5%) women were vaginally colonized with GG, despite having the GI tract colonized in 33/42 (78.6%)
Friedlander, 1986 [37]	Quasi experimental trial	38	Pre-menopausal women with h/o previous vaginal infections and treatment failure with topical and oral antibiotics	Vaginal douche	*L. acidophilus*, 10^8 - 10^9 /100ml	Daily for 7-14d with Vit B	55% of pts had normal vaginal flora at 3-6 months follow up
Reid, 2001 [34]	Quasi experimental trial	10	Women with recent h/o urogenital infection: 9/10 h/o VVC, 2 of BV, and 3 of UTI.	Oral	*L. rhamnosus* GR-1 10^9 / vial *L. reuteri* RC-14 10^9 / vial	Twice daily for 14d	GR-1/RC-14 strains were recovered from the vaginal flora in 10/10 women in 1 wk
Ozkinay, 2005 [48]	Randomized, double-blind, placebo controlled trial	360	Healthy women, both pre and post-menopausal, with genitourinary infection appropriately treated w/ antimicrobial therapy	Intravaginal suppository	*L. acidophilus* 10^7 CFU/suppository 0.03 mg estriol	Daily for 6d/ Daily for 12d (post-menopausal women)	Normal flora index increased significantly more in pts who received lactobacilli (p=.002)

RR, relative risk; CI, confidence interval

Definition of urogenital infections

In all five studies,[35,36,40,44,49] VVC was defined as presence of clinical vaginitis (i.e., vaginal irritation or itch, with or without discharge) plus evidence of yeast by gram stain or/and a positive culture for *Candida* sp. Only one study restricted the definition further by requiring the absence of concurrent bacterial vaginosis or trichomoniasis. [49]

Acute lower UTI was defined as dysuria, frequency, urgency, or nocturia, but no flank pain or fever, plus a positive screen for bacteriuria using leukocyte esterase strip [42] and/or the presence of 10^5 organisms isolated on urine culture.[32,41,43] The study by Uehara, *et al.*[33] did not specifically define criteria for UTI.

BV is classically defined either by Amsel's Criteria or Nugent's Score. Amsel's Criteria is a clinical diagnosis and includes the presence of 3 out of 4 of the following: foul (fishy)-smelling discharge, vaginal fluid pH >4.5, positive KOH amine test, and presence of clue cells in wet smear.[51] Nugent's score uses a 10-point scale based on the presence or absence of *Lactobacillus* morphotypes under oil immersion.[52] Five studies[38,50,53-55] used Amsel's criteria alone to define BV for study entry, and the remainder used both.[21,22,45] Parent *et al*,[53] however, further modified Amsel's criteria, noting a positive diagnosis with only 2 of 4 of the symptoms listed above. A relatively new diagnostic test, the BV blue test, based on the presence of elevated sialidase enzyme in vaginal fluid samples,[56] was also used in conjunction with standard criteria in two studies.[57, 58]

Description of interventions for treatment and prevention

Type of lactobacilli preparation: Most studies used intravaginal preparations of lactobacilli.[22, 25-27, 29, 31, 32, 37, 40, 41, 43-45] Four studies used oral preparations.[36, 43, 44, 57] One study used a combination of both preparations.[40] Vaginal application of lactobacilli was accomplished by capsule pessaries or suppositories, but 2 studies used douches[38,50] and one used vaginal tampons.[55] The amount of lactobacilli was specifically mentioned in all included studies, with the exception of Williams[49] and Pirotta.[40] Preparations contained no less than $1x10^6$ organisms of viable lactobacillus.

Vehicle of administration: The lactobacillus strains were placed in various vehicles prior to administration. Some studies used commercially available preparations such as Gynatren[49], Lactobac[40], Femilac®[40], Gefilus®[43], Vivag®[54] and others used non-branded products.[44,50] Colombo® plain yogurt, which ordinarily does not contain lactobacilli, was used in one study.[36] Others elaborated on specific procedures including freeze-drying with suspension in skim milk,[32,41,42] solidification with witepsol,[33] or mixture with coconut fat,[55] prior to incorporation into capsules, douche or tampon. Two studies used lyophilized lactobacilli in non-commercial medium.[38,53] The rest did not describe further, besides mentioning use of plain gelatin capsules or glycerol suppositories.[21, 22, 29, 45]

Selection and type of Lactobacillus strains: There were several strains of lactobacilli used. These included *L acidophilus, L. casei var. rhamnosus* (GG and GR-1), *L. crispatus, L. debrueckii, L. fermentum* RC-14 (re-named *L. reuteri* RC-14), *and L. gasseri*. These strains were used alone or in combination (*Tables 1-4*).

Mechanism of action: Of the 18 studies on prevention and treatment, thirteen reported on, or proposed, mechanisms of action of lactobacilli. These included 1) inhibition of candidal growth, or pathogenicity[36] either from competition for nutrients, interference with adherence, or production of bacteriocins[49] 2) re-establishment of the normal ecosystem by colonization of lower bowel and vagina to afford protection;[21,22,25-27,32, 45] 3) production of hydrogen peroxide, which provides a low pH and an intrinsic protective mechanism in the vaginal compartment;[33,44,50,53] and 4) ability of lactobacilli to adhere to uroepithelia and interfere with growth and adhesion of *Escherichia coli* and enterococci[41].

Prior antimicrobial use: Among all the studies, five[21,26,33,37,45] used a population of women who were receiving concomitant treatment with antimicrobials and lactobacilli were used as adjuvant treatment. The antibiotics included norfloxacin 400mg or trimethoprim-sulfamethoxazole 160/800 twice daily for 3 days,[42] clindamycin 100 mg ovules daily for 3 days,[55] oral metronidazole 2 g single dose[59] or 500 mg twice daily for 7 days[57]. The study by Pirotta[40] did not describe antimicrobial therapy further, except to state that patients had received antibiotics within 48 hours of entry into the study.

Duration of treatment: Treatment duration was highly variable, and ranged from four days[40] to as long as a year,[33,41,43,55] 16 months,[32] or 19 months.[49] Frequency of dosing also varied, from once daily, twice daily, every other day, thrice weekly, 5 days a week, or weekly. The frequency of dosing is shown in *Tables 1-4*.

Outcome: Cure from infection was the major outcome for all four studies on VVC.[35,36,40,49] All studies on UTI focused on prevention of infection.[32,33,41-43] The studies on BV focused on cure as the main outcome, using either Amsel's criteria,[27,31,45] or Amsel's criteria and Nugent's score[38,53,55,57, 58] for definition of cure. Two studies also commented on bacterial[54] or lactobacilli colonization[59].

For VVC, only one study by Hilton[36] showed a decrease in risk of VVC that was statistically significant [RR 0.39 (CI 0.17-0.7); p <0.009]. Similarly, only one study on UTI[41] showed a benefit either with lactobacilli [RR 0.42 (0.22-0.67); p <0.001] or the addition of lactobacilli growth factor [RR 0.628]. All the included studies of BV with the exception of three,[26,39,45] showed a statistically significant reduction in infection.

Adverse events: Adverse effects from lactobacilli preparations used for either treatment or prophylaxis were reported in seven studies.[32,33,41,42,53,55,57] Of these,

four noted no side effects, and three recorded minor complaints of headache and increased appetite,[57] or itching or burning sensations.[53, 55]

Description of studies on colonization or restoration of vaginal flora

There were seven studies that focused on colonization of the lactobacillus in the vagina or restoration of normal vaginal flora as the primary outcome.[34,37,39,45-48] Normal vaginal flora was measured using the Nugent criteria or the modified Normal Flora Index.[48] The Normal Flora Index (NFI) incorporated the number of lactobacilli, number of leucocytes, pathogenic microorganisms, and the pH of the vaginal secretions determined on a vaginal smear. Each parameter was evaluated using a four-point scale (values from 0-3) consequently resulting in a range from 0-12 for the total NFI; the higher the total score, the "healthier" the vaginal flora. Vaginal colonization was measured by serial determinations of the amount of organisms in the vagina during and following probiotic use. Lactobacilli preparations were given either orally,[34,39,46,47] or intravaginally.[23,34, 42] Four different strains were used, including *L. rhamnosus* GR-1 and *L. reuteri*, *L. acidophilus*, and *L. rhamnosus* GG. The use of *L. reuteri* [23,35,36,38] and *L. acidophilus*[34, 42] was found to improve vaginal ecology. The use of *L. rhamnosus* GG alone, at least in one study[46], had poor vaginal colonization rates, despite evidence of gastrointestinal colonization. Rate of successful vaginal colonization increased with the combination of *L. rhamnosus* GR-1 and *L. fermentum* RC-14.[45] The characteristics of these studies are shown in *Table 4*.

DISCUSSION

Our review shows that probiotics may be beneficial for urogenital infections, particularly bacterial vaginosis. Most of the included studies targeted healthy, young, non-pregnant women, and all were undertaken in the ambulatory setting.

We found considerable variability among studies in terms of choice of lactobacilli strains, which may have affected the results of the studies. There were seven strains used in the included studies. Selection of lactobacilli is particularly important, as the effect of a probiotic may be strain specific. For example, Reid and colleagues[41,60] have shown that *L. rhamnosus* GR-1 and *L. reuteri* (previously *L. fermentum* RC-14), when given intravaginally, are particularly adept at vaginal colonization and may compete against uropathogens and reduce the risk of UTI. In a subsequent study, they found that oral intake also resulted in vaginal colonization. The fact that GR-1 colonized particularly well in some patients, and *L. reuteri* in others, also suggests that the use of more than one organism as a probiotic may be useful.[34] As shown in a follow-up study in 2001, therapy with oral *L. rhamnosus* GR-1 and *L. reuteri* at $1.6x10^9$ daily dose, resulted in normalization of flora in 82% (9 of 12 patients), at 4 weeks.[39] As these strains act differently, with *L. reuteri* producing hydrogen peroxide, and L. *rhamnosus* GR-1 resisting killing by nonoxynol-9, the use of both provides a combined advantage to restoring urogenital flora.[34] The complexity of the vaginal ecosystem makes it challenging to determine what constitutes vaginal health and currently available tools are imprecise in determining this important outcome. Moreover, whether probiotics may truly colonize the vagina or represent a transient presence also needs further study.

Our review shows that among the urogenital infections, the greatest benefit with probiotics was seen in treatment of BV with the majority of studies finding a significant relative risk reduction. In one study that failed to find benefit, intravaginal tampons impregnated with multiple lactobacilli strains *(L. gasseri, L. casei var. rhamnosus and L. reuteri)* were used. The authors pointed out that this composition of bacteria, inability of lactobacilli in tampons to colonize vaginal flora, and relatively low dose of viable organisms (10^6), may have been responsible for the negative results of their study.[55]

We also found that among the different genitourinary infections we included in our analysis, little beneficial effect with probiotics was observed in VVC. Among the four studies that focused on VVC, only the study by Hilton,[36] a prospective crossover trial on prevention, showed a beneficial effect in reducing the risk of acquiring recurrent infection. In this study, a commercial preparation of yogurt (Colombo®, plain) was fortified with *L. acidophilus* at 10^8 CFU/mL. Results of the Hilton study must be interpreted carefully, however, as the trial had a significant attrition rate, with only nine patients finishing the study, due to refusal to crossover to the control arm. The lack of a probiotic effect in VVC may be explained by the choice of strain used, particularly *Lactobacillus GG. Lactobacillus* GG does not express any anti-infective proteins against urogenital pathogens,[12] has been shown to be ineffective in preventing urinary tract infections,[43] and may not be the optimal choice to prevent other urogenital infections. In a study of colonization by Cadieux *et al*,[45] there was a statistically significant difference between recovery of strains from patients treated with GR-1/RC-14 versus GG. At 14 days, GG was recovered in only 3/14 (21%), compared to 11/14 (73%) in the GR-1/RC-14 group. A similar study by Colodner[46] confirms this, with only 14.3% or 4.8% of patients given GG once or twice daily, respectively, showing subsequent vaginal colonization by the probiotic.

Only one study on urinary infections[41] showed a statistically significant reduction in infection. In this study, *L. casei v. rhamnosus* GR-1 and *L. fermentum* B-54 were used weekly for a year. There was also a significant reduction in frequency of UTIs, from 6 infections per patient per year to 1.3 infections per patient per year. Other parameters such as dose and vehicle of administration may also play a significant role and should be considered in choosing the appro-

priate probiotic preparation. In the study by Kontokiari,[43] no significant benefit was seen with use of *Lactobacillus* GG, which is likely due to its poor ability to adhere to vaginal epithelial cells, as discussed earlier. In contrast, Uehara *et al*[33] chose *L. crispatus* GA1 98332, based on its ability to produce hydrogen peroxide.[33] Although there was no statistically significant difference between patients who had infection, versus those who did not, the results of this study are promising, as there was a significant reduction in incidence rate ratio, or frequency of recurrent UTI ($p = 0.0007$). In general, most studies included a small number of patients and the possibility of a type II error is high.

Although not all studies reported on adverse effects from use of these probiotics, of the ones that did, no major side effects were observed. It is reassuring that these lactobacilli preparations, regardless of strain, and whether given orally or intravaginally, were well tolerated and caused minimal side effects. They may represent a promising alternative or adjunct to antimicrobial therapy. Future studies, however, should monitor adverse effects carefully, including the risk of bacteremia from probiotics.

Our study has several limitations. We only included studies in the English language, and restricted our search to the adult population. The studies were extremely heterogenous, and we compared results from randomized trials with nonrandomized trials. Due to the heterogeneity, a formal meta-analysis with calculation of a summary estimate was not possible.

CONCLUSION

The use of lactobacilli offers an alternative agent for use in the treatment or prevention of some types of urogenital infections. At present, the greatest evidence for use of probiotics is for treatment of bacterial vaginosis. There is little evidence to support the use of probiotics for vulvovaginal candidiasis and evidence regarding prevention of urinary tract infections is too preliminary for definitive recommendations. Further research is needed in this area. Studies should use strains of probiotics known to colonize vaginal epithelial cells, or inhibit uropathogens. Optimal dosing and duration of probiotic administration should be defined. Once these have been established, adequately powered, randomized controlled trials are needed, particularly in the areas of vulvovaginal candidiasis and urinary tract infections.

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