

Non-Antibiotic Strategies to Prevent the Recurrence of Uncomplicated Urinary Tract Infections in Women

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SUMMARY

Recurrent urinary tract infections pose a major medical health problem. In most cases, antibiotics now is recommended for their prevention and therapy on a case-by-case basis. However, the problems of an excessive use of antibiotics, e. g. resistance and long-term interference with intestinal microbiota, are forcing us to search for alternatives. The use of probiotics alone or in combination with immunotherapeutics or the sole use of immunotherapeutics are important treatment options that are already routinely available in clinical practice. These therapies are focused on the pathomechanism of an infection and tackle the root cause of the problem. Phytotherapeutics or small molecules like mannose, which restrict the adherence of bacteria to the urothelium, are complementary approaches. In the following overview we summarize a variety of non-antibiotic strategies for the therapy as well as for the long-term prevention of uncomplicated urinary tract infections according to the EAU guidelines, e.g. oral and parenteral immunostimulants (Stro-Vac), local oestrogen replacement, and administration of *Lactobacillus rhamnosus* and *Lactobacillus reuteri*. Restoring the integrity of intestinal microbiota and optimizing the immune response in recurrent infections, especially in the urinary tract, are thus treatment alternatives to the usual focus on antibiotics. Whatever therapy will be applied, the aim of all medical treatment will be *primum nihil nocere* (First, do no harm).

INTRODUCTION

In the urinary tract, for most bacteria and viruses, the first encounter with their host involves their attachment to receptors expressed by cells forming the lining of the mucosa, which results in colonization of the host prior to disease. The ability of the bacterium to breach mucosal barriers and invade the host, distinguishes pathogenic from commensal organisms. Immediate defence mechanism of the host are the shedding of uropathogens with urethral cells, the trapping of bacteria by mucus, the production of cytokines and defensins, and the mobilization of leukocytes in addition to the Tamm-Horsfall protein which is capable of both mediating direct antimicrobial activity and alerting immune cells. The flushing mechanisms and the acidity of urine also aims to maintain the bladder and most of the urethra free of microorganisms. If a pathogenic microorganism breaks the above mentioned barriers, the host immune response will prevent further attachment and abrogate colonization: macrophages, dendritic and other antigen-presenting cells orchestrate the immune defences against the invader(s). They include innate immunity (macrophages, polymorphonuclear leukocytes, natural killer cells, complement system, etc.) and the adaptative immune system with two subsystems, so the cellular immune response comprising CD4 T cells (e.g. Th1, Th2) and CD8 T killer cells, and the humoral immune response where B cells produce specific IgG, IgA, and IgM antibodies. IgA is the secretory immunoglobulin present in body secretions including urine. One major target for such antibodies are bacterial surface proteins known as adhesins, which mediate microbial attachment to host tissue. Also, the Toll-like receptor (**TLR**) family mediates immune responses; Gram-negative bacterial lipopolysaccharide (**LPS**) activates antigen-presenting cells through TLR4 whereas bacterial lipopeptides and mycobacterial lipoglycans activate cells through TLR2. TLRs can influence adaptive immune responses and exert modulating effects on Th1 and Th2 polarization of CD4+ helper cell responses [1,2].

The identification of predisposing anatomic structures and their resection as well as prudent use of antibiotics will always represent important elements in the treatment of recurrent urinary tract infections. However, this alone does not seem to improve the prevention of recurrent infections. The therapeutic approach in these cases must consider the pathomechanisms of infection more broadly. Given the fact that an infection is a highly differentiated interaction between pathogen and host, an antibiotic therapy represents a method solely directed at the pathogen. This method still characterises currently applied principles of clinical practice despite being criticized since 1992 [2] for not giving the host sufficient consideration. However, the increasing resistance that eligible pathogens are developing to antibiotics and the associated subsequent treatment failures, together with a lack of innovative antibiotic discovery, are slowly leading to a rethink [3]. Furthermore, diverse and revolutionary findings over the last few years concerning human microbiota [4] have also contributed to this rethink. Changes in clinical practice are nonetheless slow. For example, even though Gregor Reid et al [5] published a paper as long ago as 2001 ambitiously named „Oral probiotics can Resolve Urogenital Infection“

detailing a 14-day trial application of *Lactobacillus rhamnosus* and *Lactobacillus fermentum* (2 daily applications) that showed a change in vaginal milieu that significantly and sustainably reduced the risk of lower urinary tract infections, it still took more than ten years for this approach to be continued and reproduced [6]. Whereas in this first trial of therapeutic innovation only 10 patients were observed, the same team was, only two years later, able to publish a placebo-controlled prospective randomised study observing 64 patients that showed the same positive, and therefore statistically and clinically significant, findings [7]. The underlying hypothesis of these studies, namely that the vaginal milieu represents the crucial, decisive factor for urinary tract infections and especially recurrent infections, has subsequently been proved by several groups, particularly by Petricevic et al [8]. All of these studies concluded that the extent and quality of the female intestinal microbiota is pivotal to vaginal mucosal protection, with the presence of *Lactobacilli* being of particular significance [9]. Today, it is assumed that disrupted intestinal microbiota represents as major a risk factor for urinary tract infections as do the factors of genetic disposition, number of sexual contacts with different partners, and the type of sexual practices engaged in. With the production of mucus being predominantly determined by estrogen this factor must be considered as well.

Table 1: A systematic review of literature about the use of probiotics in recurrent urinary tract infections in women.

Author(s), Year	Number of Patients	Treatment, Results	Summary	Level of evidence
Abdulwahab [12] (2013)	200 (100 healthy Women and 100 isolates of women with recurrent urinary tract infections)	Cell culture of vaginal samples in asymptomatic female patients to identify <i>Lactobacilli</i> . Urine culture of females suffering from recurrent UTI on which the inhibiting effect of <i>Lactobacilli</i> on uropathogenic <i>E. Coli</i> is tested	All vaginal strains of <i>Lactobacilli</i> in asymptomatic women are able to inhibit growth on the agar plate	Moderate, Level 2
Beerepoot [6] (2012)	252	12-month prophylaxis with TMP-SMX 480 mg taken orally once daily or 109 CFU <i>L. rhamnosus</i> or <i>reuteri</i> taken orally twice a day. Primary end point: Number of symptomatic UTI, time to first UTI, development of antimicrobial resistance, proportion of patients with one or more UTIs during twelve months	After twelve months of prophylaxis the number of symptomatic UTIs decreased in women who had received <i>Lactobacilli</i> . The <i>Lactobacilli</i> did not meet the noninferiority criteria. Advantages: no development of antimicrobial resistance, improved efficacy in prophylaxis of complicated UTIs	Moderate, Level 2
Stapleton [13] (2011)	100	Daily intravaginal application of a probiotic or placebo for 5 days initially and consecutively once weekly for ten weeks. Number of UTIs and extent of colonisation with <i>L. crispatus</i>	<i>L. crispatus</i> is associated with a reduction of symptomatic UTIs	Low, Level 2

PROBIOTICS

A systematic review of literature about the use of probiotics in recurrent urinary tract infections in women [10] was carried out by PubMed. It showed 94 publications of which 12 were peer-reviewed and three were assigned a level of evidence according to the GRADE guidelines [11]. See Table 1.

The research of Abdulwahab et al [12] focused on bacteriological laboratory analyses of urine samples. They studied the effect of vaginal Lactobacilli on the adherence of *E. coli* strains isolated from 100 women suffering from recurrent urinary tract infections. In particular, they found *Lactobacillus acidophilus*, *L. fermentum* and *L. delbrueckii*. These Lactobacilli were able to inhibit *E. coli* in-vitro growth significantly. This provides additional experimental evidence that the presence of a sufficient amount of Lactobacilli can prevent urinary tract infections.

Another two publications addressed the clinical efficacy of orally and vaginally applied Lactobacilli used in the prophylaxis of urinary tract infections. In the study by Beerepoot et al [6], oral application of *L. rhamnosus* and *L. reuteri* (twice daily) showed no inferiority in the prophylaxis of recurrent urinary tract infections in 252 postmenopausal women, compared to a daily application of 480 mg TMP-SMX (Trimethoprim/Sulfamethoxazole). The mean number of symptomatic urinary tract infections in the Trimethoprim/Sulfamethoxazole group decreased from 7.0 in the preceding year to 2.9 and in the lactobacilli group it decreased from 6.8 to 3.3. This demonstrates the non-inferiority of orally applied lactobacilli, compared to Sulfonamide, as an effective prophylaxis of recurrent infection. One remarkable finding is that 100% of the *E. coli* found in recurrent UTIs showed a resistance to Trimethoprim/Sulfamethoxazole, in contrast to a total lack of microbial resistance in the lactobacilli group. The resistant *E. coli* strains persisted for 3 months up to a total number of 60%, showing not only microbial resistance to Trimethoprim/Sulfamethoxazole but also to Ciprofloxacin, Norfloxacin and Amoxicillin. Nevertheless, with 25 participants in the Trimethoprim/Sulfamethoxazole group, and 39 participants in the lactobacilli group not completing the course of therapy, this study has some limitation. Furthermore, the *Lactobacillus reuteri* colonisation of the intestine that was actually present was not shown by standard analytical methods. Another weakness of the study is the fact that a UTI was only identified by the participants themselves upon assessment of symptoms.

Stapleton et al [13] conducted a placebo-controlled study of intravaginal application of *Lactobacillus crispatus* in 100 premenopausal women. They reported a decreased rate of UTIs in those cases where a colonisation with *Lactobacillus crispatus* could be established. During the study period, 15% of the participants in the lactobacillus group and 27% in the placebo group suffered from recurrent urinary tract infection. Efficacy was especially high in 93% of the cases which showed sustainable vaginal colonisation of *Lactobacillus crispatus*, which shows that the failure of colonisation must have another reason, potentially lying in the immune response of the individual.

Taking into account all of these studies, it obviously remains difficult to determine the efficacy of probiotics in the prophylaxis of recurrent urinary tract infection. One reason being the different strains of Lactobacilli used in the studies, and the other being the lack of a standardized approach to the topic. Nevertheless, each of these studies indicates that either oral or vaginal applications of Lactobacilli are suitable for the prophylaxis of recurrent urinary tract infections. Although the effect of antibiotic therapy might occur more rapidly and might in some cases be higher, the application of probiotics, the lack of antimicrobial resistance, and the lack of influence on intestinal microbiota still remain important advantages of this therapeutic approach. Additionally, potential allergies to antibiotic substances need not to be taken into account. Confirmation of these results in the form of prospective clinical trials, compared to long-term placebo-controlled randomized trials, is still required. Until this is achieved, it is difficult to dispute the view that the second-best choice is the best.

IMMUNOSTIMULANTS

In 1996, Lettgen [14] reported in a prospective randomized cross-overstudy in children that Nitrofurantoin was not superior to an extract of devitalised immunogenic parts of *E. coli* in the prophylaxis of recurrent UTIs. They used the immunotherapeutic agent Urovaxom[®], which can be applied orally. It passes the stomach in acid-resistant capsules and dissolves in the alkaline milieu of the small bowel where its immunogenic components are absorbed by Peyer's patches. M-cells of the mucosal immune system transport these bacterial antigens and present them to the immune system. These components then bind to so-called toll-like receptors on leukocytes, which allows stimulation of macrophages and B-Lymphocytes. The antibodysecreting B-Lymphocytes travel to the mucosal immune system, among others, e.g. to the urogenital system, and produce specific antimicrobial antibodies, especially IgA, in the mucosa [15]. Metaanalyses of five placebo-controlled double-blind studies, although of relatively short observation period and of variant design, have shown the efficacy of oral immunoconditioning in the prophylaxis of recurrent UTIs [16]. A breakthrough in terms of acceptance of Urovaxom[®] use for immunoconditioning and prophylaxis of recurrent UTIs was achieved by a multicentre double-blind study by Urovaxom[®] in 2005. In this study, 435 women were randomised creating a Urovaxom[®] group and a placebo group. In the verum group, UTI recurrence was reduced by 34% in comparison to the placebo group. The period of treatment was 90 days, followed by a 30-day break and a boosting period of ten days in the months 7, 8 and nine. The follow-up period was 12 months in total [17]. With Urovaxom[®] stimulating the mucosal immune system through an immunogenic fraction of *E. coli*, the most recent research shows even higher efficacy in the oral or sublingual application of combined immunogenic fractions of *E. coli*, *K. pneumoniae*, *P. vulgaris* and *Enterococcus faecalis*. In a multi-center observational study, 159 patients received immunoconditioning with Uromune[®] and 160 patients with SMX/TMP over a period of six months. Recurrence rates were significantly lowered by immunoconditioning after 3, 9 and 15 months ($p < 0,0001$), namely 75% after 3 months, 86% and 77% after 9 and 15 months respectively [18]. Another retrospective cohort study was

conducted with 669 women suffering from recurrent UTIs. 339 patients received an antimicrobial prophylaxis (SMX/TMP or Nitrofurantoin) over a period of six months and 360 patients were treated with a sublingual immunogenic specimen (Uromune®). After antibiotic prophylaxis, all patients suffered from a recurrent infection after the first 12 months, whereas this only occurred in 9,7% of the patients in the immunoconditioned group [19].

Without a doubt these results need further confirmation in the form of a prospective randomised trial, ideally a placebo- and antimicrobial- controlled study.

Apart from oral immunoconditioning, the option of parenteral immunoconditioning remains, e.g. StroVac® (Perison®, SolcoUrovac®), where bacterial fragments are applied parenterally. This however leads to an emphasis on the side effects compared to oral immunoconditioning. In the original package leaflet of StroVac® local reactions to vaccinations are said to have occurred in 10% of cases. Systemic reactions such as fatigue and flu-like symptoms seem to occur to the same degree [20]. StroVac® consists of 10 inactivated pathogens of 10 strains belonging to five species (*E. coli*, *Proteus mirabilis*, *Proteus morganii*, *Klebsiella pneumoniae* and *Enterococcus faecalis*). Basic immunisation consists of 3 i.m. injections with an interval of one or two weeks between sessions. A booster vaccination can be applied after one year [21]. After immunisation, not only an increase of secretory immunoglobulin in mucosal tissue can be seen, but also an increase of IgG in the blood, both of which represent a characteristic of parenteral immunisation. In several controlled trials the rate of UTIs decreased by 26-93% in comparison with the placebo trials [22]. In addition to oral and parenteral immunization, even vaginal immunisation is possible. Currently there is no commercially available product for this use. Studies to date have been conducted using Urovac®, a vaginal vaccination administered in the U.S. This vaccination contains 10 different, heat- inactivated uropathogens like *E. coli*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Morganellamorganii* and *Enterococcus faecalis*. In this case, too, different classes of Immunoglobulins such as IgA and IgG are stimulated [23]. A meta-analysis of three studies conducted with Urovac® shows a decreased risk of recurrence but not a significant one versus a placebo. One limitation is that 27.8% of the women showed vaginal irritation after use of the suppositories. The suppositories were applied once weekly over a period of three weeks. Two different studies then used 3 monthly booster applications. The results of booster immunisation were superior to basic immunization [24].

The development of a parenteral immunisation against *E. coli*, consisting of four different antigenic epitopes of different *E. coli* arouses great interest. Initial experiments involving animals seem to be promising. Immune response in this case consists solely of the stimulation of IgG immunoglobins that bind exclusively to uropathogenic *Escherichia coli* (**UPEC**) pathogens. Nevertheless, this gives rise to something of a contradiction concerning the necessity of mucosal protection for preventing female lower UTI and its pathomechanism [25].

CRANBERRY EXTRACTS

In the prophylaxis of recurrent UTIs, cranberry extracts, fluid cranberry or cranberry tablets are already available in current clinical practise. Especially in the U.S., cranberries have been used in prevention of UTIs for many years [26]. The mechanism of action still seems to remain unclear. Cranberries contain a Proanthocyanidin type A (**PAC**), which inhibits the adhesion of *E.coli* P-fimbriae to the urothelium. Some studies from 2011 show that a six-week application of cranberry extract leads to a change in intestinal microbiota, especially to an increased number of bifidobacteria and lactobacilli. This also suggests a mechanism of action that influences intestinal and vaginal microbiota [27]. The last Cochrane report (based on 24 studies and 4473 participants) about the use of cranberries in the prophylaxis of UTIs did not show a significant difference between cranberry products and control groups. Nevertheless a trend towards the use of cranberry products can be seen [28]. In cranberry groups, there was a high number of drop-outs due to adverse effects. Cranberry juice is often characterised as bitter and not easy to digest. This problem has been resolved in a new but not yet established preparation (CranBlue®, daily dose no less than 40 mg PAC). It seems to be important that products containing Cranberry only have a half-life period of 12h and therefore have to be applied twice daily. A comparison of different studies remains difficult, because the required dosage is still unclear or rather because there are still no dosage-dependent studies proving adhesional effects in the human system. The target content of Proanthocyanidine (**PAC**) should probably be a daily dose of 72 mg [29].

The comparatively high content of oxalic acid in products containing Cranberries, especially in cranberry juice, and related berries could be problematic. Patients prone to oxalate stones are at risk [30]. The possibility that synergistic effects caused by fructose, e.g. in cranberry juice, could enhance efficacy is only speculative, even though it is known that fructose itself inhibits the adhesion of *Coli* bacteria.

ESTROGENS

Medication with estrogen plays an important role due to estrogen-dependent mucus secretion of the mucosa, especially in the peri- and postmenopausal phase, where estrogen levels drop [31]. Oral application of estrogen could not lower the risk for recurrent UTIs and had negative effects on efficacy as individual studies and the meta analysis showed. However, vaginal application of estrogens, especially of estriol, remains an important method of lowering the risk of recurrent UTIs in peri- and postmenopausal women [32]. Susceptibility to infections could be reduced to 0.5 episodes per year, compared to 5.9 episodes in coeval women, by local application of estriol. This advantage could be proven from comparisons with placebos [33]. Estriol, a metabolite of estradiol, does not show any effects on the endometrium, and due to its short binding period to the estrogen receptor there is no need for combining it with gestagens. According to some Scandinavian studies there also is no risk of thromboembolism or a higher rate of breast cancer [34]. The working group hormones of the society of Gynecology recommends a topical ultra low-

dose application of 0.03 mg of estriol (not estradiol) for vaginal atrophy after breast carcinoma, especially under treatment with tamoxifen, if non-hormonic measures fail [35]. Experimental data show that estrogenisation of peri- or postmenopausal vaginal epithelial cells leads to increased networking and therefore more densely connected vaginal epithelium. At the same time, gene expression of antimicrobial peptides is enhanced. Both mechanisms are of particular importance for the protection of the vaginal epithelium [36]. However, vaginal application of estrogen can lead to local irritation in up to 20% of cases. Our findings show that this can be caused by a vaginal dysbiosis which makes the patients see their doctor. These patients should be diagnosed and treated before local application of estrogen.

Due to the pathomechanisms discussed, the application of lactobacilli alone does not lead to a satisfying result.

URINE ACIDIFICATION

Data concerning urine acidification in recurrent UTIs are inconsistent, and have not yet met the expectations placed on them. Renal insufficiency, hyperuricemia, metabolic acidosis, as well as uric acid stones, cystin stones and homocystin stones represent contra-indications for this method [37].

MANNOSE

In a three-pronged prospective controlled open clinical trial, the rate of UTIs could be lowered significantly by the application of 2g of mannose compared to a placebo. Mannose is a monosaccharide inhibiting the adherence of some bacteria to the urothelium. A mannose-specific lectin receptor was found in *E. coli* strains. Application of mannose seems to be a cost-effective, often neglected alternative method of lowering the risk of recurrent UTIs. Increased flatulence could be the major problem of therapeutic mannose use [38].

PHYTOTHERAPEUTICS

There are many years of experience in the use of plant extracts in the prevention of recurrent UTIs. However, there is little data available concerning these products. Study designs meeting today's criteria are scarce. Most of the time, we find only short-term follow-ups or observation studies. However, the combination of mustard oil derived from nasturtium with horseradish (Angocin®) is worth mentioning in this context. Recurrence rates in 103 patients could be reduced from 0.77 in the placebo group, compared to 0.43 in the verum group in the 180-day follow-up. Due to the low spread of the data the results remain insignificant, but show a positive trend. A high rate of side effects of 43%, and 41% respectively limits the study's importance. Bearberry leaves in combination with dandelion, as well as nasturtium with horseradish could lower the rates of recurrent UTIs. Similar results were seen for centaurium, lovage and rosemary [39,40].

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