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# Recurrent Urinary Infections

**Nuria Orozco Mossi* and Gloria Rabanaque Mallén**

*General practitioner and member of the group of infectious diseases SEMFYC of Valencia, Spain*

***Corresponding author:** Nuria Orozco Mossi, General practitioner and member of the group of infectious diseases SEMFYC of Valencia, Spain

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ABSTRACT

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## Introduction

The aim of this article is to talk about the scientific evidence that exists in relation to the development of vaccines as a strategy for the management of recurrent urinary tract infection (rUTI) in non-pregnant women. Before entering in this matter, it is important to introduce some aspects which are crucial to understand the research process for these alternatives which try to rationalise the use of antibiotics in urinary tract infections (UTI). Approximately 50-80% of the woman, will suffer from ITU during lifetime, and around 30-44% of them will have at least a recurrency annually [1]. The definition of recurrency in nonpregnant woman refers to 2 or more infections in a period of 6 months, or more than 3 in a year [2]. It is important to distinguish between relapse and reinfection. A relapse is the infection caused by the same strain of microorganism than the one responsible for the original infection and occurs within the first two weeks after completing the treatment for the original infection. It is about 20% of all the rUTI. Reinfection occurs when a different strain of microorganism causes a UTI being 80% approximately of all the recurrences [1,3].

The pathogenesis of rUTI is similar to UTI. Around 68-77% of recurrences are caused by E coli showing no different strains from those that caused previous infections.1,3 There are many factors which have been considered risk factors, but not all of them have proven evidence. It has been demonstrated on clinical trials, that the use of spermicides or diaphragm are strong independent risk factors for rUTI. Being sexually active also results in an increased risk this [4,5]. There are pelvic anatomic factors which can favour rUTI, for example having a short distance between urethra and perine, given that the migration of bacteria in vaginal region can occur easily. Genetic determinants appear to account for rUTI in some women. The low expression of the CXC chemiokine favours rUTI. This chemiokine is in charged of favouring neutrophil migration to the infection site. When patients have a low expression of this chemiokine, there is a higher tendency to develop rUTI and recurrent pyelonephritis [3,6].

There are other factors which have been identified as risk factors, but studies have not proven to be highly effective in reducing the risk of rUTI. These factors would be postcoital urination, postcoital shower and use of cotton underwear to prevent UTI, and caffeine consumption, sexually transmitted infection background, use of tampons, bicycle riding or having a high body mass index would predispose for UTI [1,6]. When referring to the use of cranberry as a strategy of prevention, there is weak evidence supporting its effectiveness However, the use of topic oestrogen. The use of topical oestrogen therapy has around a 30% effectiveness in post-menopausic woman with atrophic vulvovaginitis. The treatment would be one single application daily for 2 weeks, and afterwards three times weekly for 8 months [7].

## Management

### What are the Recommendations for rTUI in Terms of Imaging, Urine Analysis and Treatment?

It is always important to be able to rule out urological abnormalities by means of an abdominal X-Ray or an echography, however there are variations in guidelines as to when it is necessary to request these image tests. Recommendations are made by groups of experts. The Canadian Urological Association Guideline recommends image tests in patients with personal history of surgery, kidney stones, anatomical abnormalities, multi-

resistant organisms, haematuria, fecaluria, microscopic haematuria after of treatment [8]. As for the utility of urine culture, there seems to be consensus on the importance of doing a urine culture before initiating treatment, and 7-15 days after having finished it. The aim of this, is to confirm diagnosis, assuring that the treatment prescribed is effective, and finally making sure that the infection has been cured or if the patient has a reinfection or relapse [4,6].

When having rUTI one of the most important decisions to make is whether the patient will use continuous prophylaxis, postcoital prophylaxis or an intermittent self-treatment when the patient starts with symptoms. The third option has de advantage of minimizing the exposure to the antibiotic and therefore the possibility of generating bacterial resistance or adverse effects. To be able to use this strategy, it is important for the patient to have a high control of her symptoms, too be motivated and compliant with medical instructions. These patients will start treatment whenever symptoms appear, knowing that if new symptoms appear or if these are not resolved after having taken treatment for 48hours, the patient should seek for medical advice. (this has an evidence 2b and recommendation A by the European Association of Urology of 2017) [5]. In 2014 Prescrire published an article that said "The amount of antibiotic used when fosfomycin trometamol is taken every 10 days for 6 months is equivalent to treatment of 18 acute episodes of cystitis" with tends to support the trend of treating each episode [9]. However, UpToDate in 2018 suggests "Continuous prophylaxis, postcoital prophylaxis, and intermittent self-treatment (which is not really a prophylaxis method) have all been demonstrated to be effective in the management of recurrent simple cystitis.

The choice of approach depends upon the frequency and pattern of recurrences and patient preference"[6]. If the patient relates UTI with sexual intercourse, postcoital prophylaxis can be a good option. A single postcoital dose after sexual intercourse could be effective. Depending upon the frequency of intercourse the patient could take 3 tablets weekly, or if intercourse is not frequent this strategy could decrease the antibiotic consumption [1,6] The use of continuous prophylaxis has a duration of 6 months and after this time, tolerability and response is assessed. If prophylaxis has been effective, no more antibiotic is needed, but if it has not, prophylaxis can be extended to 1-2 years [1,5,6].

To select the correct antibiotic in rUTI, it is important to have previous urine cultures to know the susceptibility patterns of the strains causing the patient's previous infections. It is also important to know the patient's tolerance to antibiotics and the percentage of resistance to them in the area we are working in. Ideally, we should choose the antibiotic with most narrow spectrum with the intention of avoiding as much as possible the development of bacterial resistances, that is one of the emerging problems nowadays. It is also important to take into account considerations on antibiotic toxicities, especially when there is going to be a long-term exposure of these, such as continuous prophylaxis with nitrofurantoin, as pulmonary fibrosis, or chronic hepatitis, have been described or fluoroquinolones and muscle and tendon problems [10-14].

## Vaccines

Focussing now on vaccines. To be able to write about this topic, we decided to make a bibliographic research to know why and when the idea of vaccine treatment in rUTI arises, and how the development has been over these years. The first article published on this topic was in 1926. From then on, there are hardly 420 articles, which include 29 clinical trials and 3 meta-analysis. In 1926 the pathologist TH Benians talks about the needs of stimulating the immunitary genitourinary tract by means of inoculating the dead bacillus subcutaneously with the intention that the body will secrete specific IgA and IgG against the bacillus [15]. After this first article, and especially since 1984, 2-3 articles were published annually. They discussed the possibility of combining oral antibiotics with vaccines composed of specific IgG against de bacillus with the purpose of stimulating as much as possible, the immunitary system by generating innate and adaptative immune responses. After 2012 investigation on vaccines increases rapidly, publishing 19 articles per year until nowadays.

Globally, and to summarize the contents of the three meta-analysis published in 2009, 2013 and 2014, we have 2 different vaccines. An oral vaccine and a vaginal vaccine. The oral vaccine OM89, is made from an extract of 18 different serotypes of heat-killed uropathogenic *E. coli*, which stimulates innate immunity by the upregulation of dendritic cells which throughout Toll receptors will increase the arrival of neutrophils, and phagocytosis of macrophage [7,16]. The conclusions of the meta-analysis show benefit in favour of this vaccine in short-term follow up, but with a high heterogeneity in the data analysed [7,16,17]. The most relevant studies with this oral immunostimulants are a multicentre, double-bling study carried out in 2005. A total of 453 patients with rUTI were treated. 231 patients received the immunotherapeutic OM 89 and 222 the matching placebo. Every patient took 1 oral tablet daily for 90 days, then 3 months without treatment and then, another tablet daily during the first ten days of the months 7, 8 and 9. There was a follow up of 12 months. The results showed that mean rate of post-baseline UTIs was significantly lower in the active group than in the placebo group (0.84 vs. 1.28; p: 0.0026), corresponding to a 34% reduction of UTIs in patients treated with OM-89. Also, in the active group, 93 patients (40.3%) had 185 post-baseline UTIs, compared to 276 UTIs in 122 patients (55.0%) in the placebo group (p=0.001) [18]. In a more recent article in 2010 the sample group was of 42 patients with rUTI. All the 42 patients took a tablet daily for 3 months; women who suffered UTI during theses 3 months were excluded from the study. After the treatment, the was a follow up of 6 months.

The purpose of the study was to measure the efficacy of the vaccine by comparing the number of episodes of UTI during the 6 months after treatment compared to those during the 6 months

before treatment. The results showed a significantly lower number of recurrences after the treatment compares to the 6 months preceding the trial (0.35 vs. 4.26, P<0.001) [19]. Another vaccine is the vaginal vaccine. Only 2 out of the 3 meta-analysis investigate on the effectiveness of the vaccine, concluding on a slightly reduction on the rUTI rates, when administered with a booster cycle [7,16]. The use of this vaccine is based in the existence of mucosa-associated lymphoid tissue (MALT) on the urogenital tract which would be able to recognise bacterial antigens and generate a local immune response generating the production of IgG and IgA in the urogenital tract, reducing therefore the colonisation of uropathogens in vagina and bladder. This vaginal vaccine contains 10 heat-killed uropathogenic bacterial species, including four different serotypes of uropathogenic *E. coli*, and one strain each of the following: *Proteus Vulgaris, Klebsiella Pneumoniae, Morganella Morganii* and *Enterococcus faecalis*. The administration is by means of vaginal suppositories [7].

The most relevant studies are 2, both randomized, double-blind, placebo-controlled trials of vaginal mucosal immunization which include pre and post menopause woman with rUTI. The first one in 1997, was a phase II study with 91 women. They received 3 vaginal suppositories at weekly intervals (primary immunization) and then, a follow up of 20 weeks to record infection episodes and obtain urine, vaginal irrigates and serum to measure immunological responses. The results of the study show that there was a delay in interval to reinfection in the vaccine group compared to the placebo group. Mean interval until reinfection was delayed from 8.7 weeks for placebo treated to 13 weeks for vaccine treated women (p:0.45). What was significantly lower was the frequency of UTI during the first 4 weeks after receiving the treatment in the vaccine treated women compared with the placebo group: 9% vs 47% p:0.003 [20].

In another study in 2007, patients were randomly assigned to receive placebo only, primary immunization, or primary immunization plus booster, which consists of taking 3 vaginal suppositories at weekly intervals and after, one vaccine per months the next 3 months (6 vaccines on the global count). All women were monitored for 6 months to record the number of infections and adverse effects during that period. Results showed significantly less recurrency rates in women given booster immunization compared to placebo (72,5% vs. 30% p: 0.0015) these results were more notorious on sexually active women, <52 years, who had not undergone hysterectomy. The investigators explain this difference, by the possibility of a reduction in the immunity tissue of the cervix after surgery and after the age of 52 [21].

There is only one clinical trial comparing oral prophylaxis with vaccine treatment and its superiority or non-inferiority in 2012 with 319 patients. 159 received oral vaccine for a period of 3 months (group A) and 160 with sulfamethoxazole/trimethoprim 200/40 mg/day for a period of 6 months (group B). The patients receiving the vaccine had a smaller number of UTI than those receiving antibiotic in the first 3 months, the mean number of infections was 0.36 versus 1.60 (P < 0.0001), in group A compared with group B, during the 15 months of follow up. The results over time tended to be equal [21].

## Conclusion

Although, studies with OM-89 appear to have good internal and external validity, as ad-mission or exclusion criteria were relatively broad16 there are no data beyond 12 months. No longer follow up has been done, so it is difficult to draw long term conclusions. Clinical trials show that immunological memory tends to decrease after time, so further studies have to be conducted evaluating long-term efficacy [17]. Vaginal vaccine has been shown to be effective only when administered with a booster cycle in three small phase II trials16, but also, no long-term efficacy has been evaluated and larger and better-defined studies of this vaccine should be performed to be able to extract solid conclusions on the real effectiveness of the vaccine.7 Some of the methologies used for both vaccines, regarding the method of randomization, or description of out-puts were not described in some of the clinical trials used in the meta-analysis. These factors reduce the quality of the studies analysed and therefore put in doubt the validation of the meta-analysis

Only one of the articles declares to have no conflict interest, another was funded by the pharmaceutical industry and the other one has no declarations on interest conflict. The meta-analysis which was very much funded by the pharmaceutical industry, included data that did not come to be published in reviewed journals, which makes the conclusions doubtful. Also, no negative results regarding the use of OM-89 have been published which could mean that some data has been discarded and not published (publication bias)17 At this stage, vaccines are in the process of becoming a useful therapy for rUTI, but the absence of strong evidence, explains why they still do not appear as a strategy for the management of recurrent urinary tract infection in clinical guidelines, and they are only named as promising therapies[1-10].

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