# INTRODUCTION TO THE BURDEN OF RECURRENT CYSTITIS AND RATIONALE FOR PREVENTION

## Narrative Summary of Selected Presentations given at the OM Pharma/Vifor Pharma URO-VAXOM® Summit, held in Buenos Aires, Argentina, on 26th–27th April 2014

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## SUMMARY

This educational summit, supported by an independent grant from OM/Vifor Pharma, brought together experts in the field of urology and gynaecology from Europe and Latin America to meet and discuss the cutting edge management of patients suffering from recurrent urinary tract infections (rUTIs). The meeting included plenary lectures as well as workshops and interactive sessions, allowing delegates and presenters to debate the most pressing international and local issues in the field.

50% of women experience at least one UTI in their lifetime; 25% and 44% of these patients will suffer recurrence of infection within 6 months and 1 year, respectively. It is estimated that rUTI affects up to 10% of otherwise healthy women.[1] Data from epidemiologic studies suggest that each episode of acute cystitis in young women is associated with approximately 6.1 days of symptoms, 2.9 days of restricted activity, 1.2 days of inability to attend classes or work, and 0.4 days of bed rest. This may represent a burden for the patients. Furthermore, the management of each repeated infection leads to healthcare system expenditures. Given the level of prevalence and recurrence, assessment of the burden of UTI at both an individual and societal level and the identification of prophylactic measures to ameliorate this burden are essential for the effective management of rUTI.

## COST OF UTI

Data from Latin America are sparse; however, the annual treatment cost of uncomplicated UTI in the USA is estimated at $1.6 billion.[2] Over 7 million UTI-related medical visits occur per year, including >2 million visits due to cystitis and 270,000 urological consultations. >11.3 million women in the USA suffer ≥2 bouts of cystitis, with the consequent need for antibiotics. Annual costs for antibiotic treatment is >$1 billion, and total direct and indirect costs are >$2 billion.[1,3] >100,000 UTI-related hospital admissions, mostly due to pyelonephritis, occur annually.[2,4] Although the risk of progression from cystitis to pyelonephritis is low (<1%) in healthy individuals there is higher risk in some groups, such as pregnant women and young children.[5] The risk of hospitalisation in patients with pyelonephritis runs from 10–30%, and the estimated costs of this condition in 2013 were $2.9 billion.

### Socioeconomic Burden of UTI

The recently conducted GESPRIT (Germany, Switzerland, Portugal, Russia, Italy) study has used

an innovative online patient-focused methodology to assess the socioeconomic impact of rUTI from the patients' perspective. The GESPRIT study was a single time point, internet-based study with questions designed to address the impact of rUTI on the quality of life (QoL) and socioeconomic factors. Data were collected from five countries: Switzerland, Italy, Germany, Poland, and Russia. The target group for the study was women ≥18 years of age; with a history of ≥2 UTIs in the last 6 months or three within the last 12 months; whose previous UTI exhibited two clinical symptoms indicative of lower UTI; and who were either acutely infected at the time of survey or had their last infection within the preceding 4 weeks. GESPRIT used an author-designed questionnaire approved by experts in urological infections.[6] Recruitment was via online advertisement and the web-based survey which addressed female patients only was available between 26th August 2013 and 14th October 2013. Questions covered demographics; self-reported disease history; antibiotic use and prophylaxis; burden of illness according to patient judgment; QoL (SF-12 questionnaire); and other personal patient characteristics (e.g. marital status).

### Impact of rUTI data from the GESPRIT study

In total, 107,244 individuals began the survey: 40% directed from Facebook/Vkontakte, 34% from Google Display, 19% from the ClinLife database, and 8% from other sources. Attrition rate was high; however, the survey still achieved an impressive completion rate of 1,932 valid participants (1,269 acutely infected, 663 infected within the last 4 weeks). Geographic distribution was well balanced with around 300 patients included from each country. Annual incidence of UTI ranged from 3–12 episodes, with a median of 4–5. Recurrence rate was not age dependent; this is notable given our knowledge of age-related risk factors. rUTI was a long-term problem in the population, median 5–9 years, older patients reported a longer duration of illness. The majority of respondents were, as expected, otherwise healthy, although a small contingent had concomitant diabetes mellitus. Close to one-third (30%) of participants were post-menopausal. As expected, the most frequent symptoms were frequency, urgency, and dysuria. Some patients reported typical signs of upper UTI infection such as flank pain and fever.

The median number of sick-leave days was 1–2; neither educational nor income level appeared to be related to the number of sick days taken. Economic factors appear to impact on patients' treatment decisions as the willingness for respondents to incur out-of-pocket expenses for preventive measures was dependent on income. Medical visits differed significantly between countries, with Germany having the highest attendance (mean visits to doctor 4.71) and the lowest in Italy (mean visits to doctor 3.18). In Russia, the majority of medical visits were to the hospital (65.6%), and visits to the emergency room were frequent; Poland had the lowest proportion of hospital visits (26.7%). The route of these differences likely lies in alternative health service structures. Given the number of sick days and doctor visits, the burden of rUTI on women in the GESPRIT study appears to be high.

## UTI AND QOL

The topic of QoL in patients suffering rUTI has been severely undervalued. However, anecdotal evidence from the clinic indicates that rUTI can have a major impact on QoL. Measuring QoL is not only an important indicator of the symptom burden upon patients but also serves as a measure of the true impact of treatment and preventive measures. Until recently there have been no published studies focusing on the impact of rUTI on QoL or how QoL may be modulated by treatment or preventive measures, despite data from epidemiologic studies supporting this.[2]

### Recent Data on UTIs and QoL

As mentioned earlier, the GESPRIT study evaluated QoL alongside socioeconomic factors in women with rUTIs. In addition to some general questions, a specific questionnaire to assess QoL - the SF-12v2 questionnaire - was used in this study. This is a validated, 12-item questionnaire, covering both physical and mental areas (8 physical and 4 mental health aspects). The scoring methodology is simple and has been standardised against the general population in the USA in 1998 (mean= 50 and SD=10). Despite not being a specific questionnaire to assess QoL in the specific medical condition of rUTI, the SF-12 has the advantage of having been widely used to assess individuals with different conditions, allowing comparison of scores and QoL indicators. The main findings of the GESPRIT study are that 30–50% of females with rUTI felt restricted in doing everyday life activities. Emotional disturbances were frequent, including depression and anxiety.

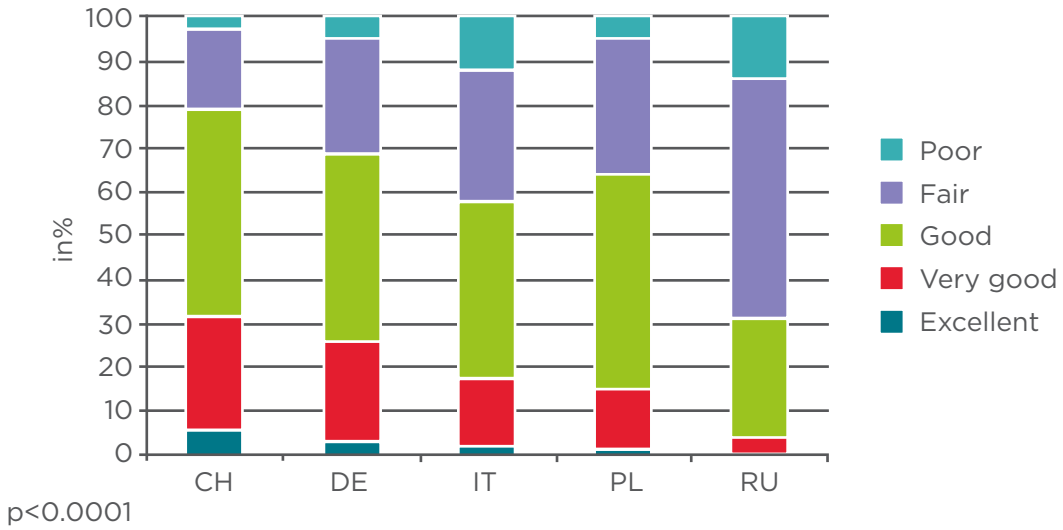


**Figure 1: Respondents' general feelings about health.**
CH: Switzerland; DE: Germany; IT: Italy; PL: Poland; RU: Russia.

Many respondents described anger, disappointment, and frustration.

Respondents from Russia reported the most negative feelings regarding general health, with the majority describing their health state as fair or poor (Figure 1). Results from the SF12v2 questionnaire showed a significant impact of rUTI on respondents' QoL. In patients with acute infections at the time of the survey, both mental and physical states were affected with some countries' specificities. More interestingly, in the group of patients not infected with a UTI, but having had the last recurrent infection in the previous 4 weeks, a reduction in mental health persisted. This suggests that rUTI has a detrimental chronic effect, mainly on patients' mental wellbeing, and impairs their QoL.

Alongside GESPRIT, another observational study has been conducted to address the impact of rUTI on QoL. The HARMONY study was a prospective, observational, multicentre study conducted in 151 centres across 7 countries (Egypt, Germany, Lebanon, Peru, Poland, and Switzerland). Patients were enrolled from multiple healthcare settings with participating investigators including urologists, gynaecologists, internists, and primary-care physicians. Patients were ≥18 years old, with ≥3 UTI episodes in the last 12 months, for whom preventive treatment using long-term medication was planned. Participants received optimal prophylaxis according to best standard of care, which included oral immunostimulant OM-89.

In order to assess QoL, two questionnaires were used: the Hospital Anxiety and Depression (HAD) questionnaire[7] and the Leicester self-assessment questionnaire.[8] The HAD and Leicester questionnaires have undergone validation for their sensitivity in detecting anxiety and depression in patients with mental and somatic conditions and QoL in patients with urinary symptoms, respectively.[7,8] Questionnaires were completed at study entry before the beginning of prophylaxis, and at 180 days, to allow evaluation of the effect of an effective prophylaxis on patient QoL.[9] In total, 575 patients underwent assessment and filled in a questionnaire. At baseline, the majority of participants (62%) had a global HAD score indicative of minor depression or anxiety. Three-quarters of patients (74%) exhibited symptoms of anxiety and 36% showed symptoms of depression. Disturbance to daily life, as measured by the Leicester scale, was reported by 74% of participants, with almost as many patients presenting minor social or functional limitations. Close to 60% of patients expressed troubled feelings related to their rUTI,[9] indicating a significant impact of rUTI on QoL.

## QoL, Treatment, and Prophylaxis

Attitudes to antimicrobial therapy appear to differ geographically. Data from the GESPRIT study showed that in Russia and Poland antibiotics were viewed as powerful therapies. Respondents reported a desire to manage their illness without antibiotics where possible, and were very open to

other therapies. Respondents from Germany, Switzerland, and Italy felt that antibiotic therapies were necessary but reported concern over loss of efficacy. Therefore in both cases some reluctance toward the antibiotic use has been shown. Prescribing patterns also varied, with patterns reflective of respondent attitudes (Figure 2). GESPRIT participants reported a high willingness to take prophylactic measures against UTI. The vast majority (80%) of patients had tried several preventive measures in the past; however, four to five per year was the median number of UTIs that patients suffered before being recommended preventive strategies by their physicians.

In the HARMONY study there was a highly significant decrease in the number of UTIs (59%, p<0.0001) following 6 months of best-standard-of-care prophylaxis. This effect was consistent across countries and centres. Prophylaxis had a positive effect on both the anxiety and depression (36% and 25% reductions in anxiety and depression components of the HAD score, respectively). The 32% overall reduction in HAD score was highly significant compared with baseline (p<0.0001). Participants also reported improvements in terms of daily activity (33%) and troubled feelings (55%), with a highly significant reduction in overall Leicester score (44%, p<0.0001) compared with baseline.[9] The improvements in depression, anxiety, and global HAD scores were significantly correlated with the reduction in the mean number of UTIs (p<0.0001). Similarly, there was a significant correlation between the reduction in cystitis occurrences and improvements in 'troubled feelings' (p<0.0001) and overall Leicester scores (p=0.02).[9]

## NON-ANTIMICROBIAL PROPHYLAXIS

The need to reduce the burden of rUTI in terms of both socioeconomic and QoL factors is clear. Women suffering rUTI appear to be a motivated patient group and are keen to undertake prophylactic measures also to avoid antibiotic collateral damage and potential side-effects. The most common general prophylactic measures attempted by women in the GESPRIT study (such as voiding before or after intercourse, diet, increase of water intake) did not prevent recurrences. The HARMONY study shows that best practice prophylaxis improves recurrence rate and therefore QoL. Hence, there is a need for physicians to establish a rigorously evidence-based understanding of prophylactic measures and pass on this knowledge to their patients. A number of non-antimicrobial therapies have been studied in trials of rUTI prophylaxis including: ascorbic acid (vitamin C); cranberry; lactobacilli; oestrogens; methenamine salts; OM-89; and the vaginal vaccine Urovac®. Here we will briefly ummarise the evidence of efficacy for each of them.

### Prophylaxis with Ascorbic Acid

The rationale behind the use of ascorbic acid as a rUTI prophylactic is that it may act as a urine acidifier, creating a less favourable environment for uropathogens. Only two trials have been conducted investigating the efficacy of ascorbic acid prophylaxis in UTI with conflicting results.[10,11]

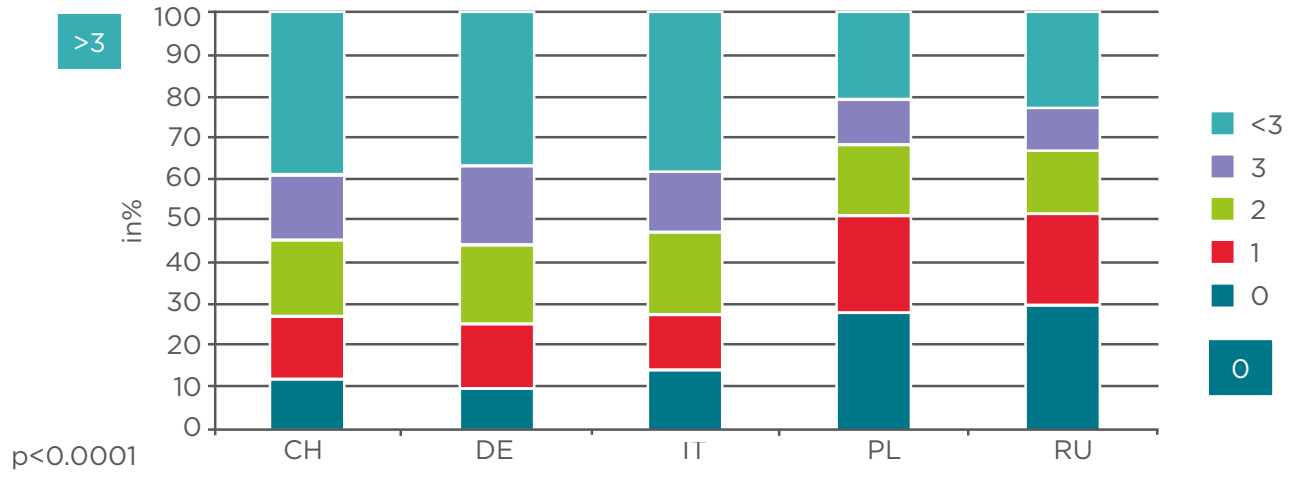


**Figure 2: Number of antibiotic prescriptions received in the last year for urinary tract infection.**
CH: Switzerland; DE: Germany; IT: Italy; PL: Poland; RU: Russia.

The first study was conducted in 38 spinal cord injury patients, a group at high risk of UTI due to neurogenic bladder syndrome. Patients were randomised to receive 500 mg of ascorbic acid four times a day or placebo. There was a high attrition rate in the trial (66%) and no reduction in urinary pH was attained. Two patients in the ascorbic acid group and one in the placebo group had a UTI; no significant treatment benefit was detected.[10]

The second trial was a non-randomised, single-blind study, carried out in pregnant women. Participants received 100 mg of ascorbic acid or placebo alongside ferrous sulphate and folic acid supplements for 3 months. Authors reported a reduction in UTI incidence in the ascorbic acid group compared with supplementation without ascorbic acid (12.7% versus 29.1%, respectively). Methodological issues including: lack of double-blinding and randomisation; lack of microbiological controls; subjective symptom evaluation; and low dose of ascorbic acid, affect the validity of results from this trial.[11] What evidence there is of efficacy in prophylaxis is poor quality and, therefore, use of ascorbic acid cannot be recommended.

## Prophylaxis with Cranberry

Cranberry products have been used for many years for the prevention of UTI. The mechanistic rationale is that Type A proanthocyanidins (PAC) inhibit P fimbriae of *Escherichia coli*, which are key for adhesion to the uroepithelium.[12] A large meta-analysis of studies on prophylaxis using cranberry has been carried out by the Cochrane Collaboration and was recently updated with new data from 14 studies (24 studies with 4473 participants).[13] Before this recent data update, results showed some benefit of cranberry juice in preventing UTI. Following the update, results showed no benefit of cranberry prophylaxis either versus antibiotics or versus placebo. Authors concluded that cranberry products did not significantly reduce the occurrence of symptomatic UTI overall (RR 0.86, 95% CI 0.71–1.04). Neither were there positive effects in any of the subgroups analysed: women with rUTI (RR 0.74, 95% CI 0.42–1.31); older people (RR 0.75, 95% CI 0.39–1.44); pregnant women (RR 1.04, 95% CI 0.97–1.17); children with rUTI (RR 0.48, 95% CI 0.19–1.22); cancer patients (RR 1.15, 95% CI 0.75–1.77); and people with neurogenic bladder or spinal injury (RR 0.95, 95% CI 0.75–1.20).[13]

The authors conclude that current evidence does not support the cystitis-preventing potential of cranberry juice. The majority of studies indicate that any possible benefit is likely to be small and that adherence to therapy was poor. Therefore, authors state that further studies of cranberry juice should not be undertaken without strong justification, given the likelihood of similar results in support of this conclusion. In the case of other cranberry products such as tablets and capsules, authors tentatively support further research for women with rUTIs, with carefully assayed treatments containing 36 mg/day of PAC.[13] In summary, there are conflicting results on the efficacy on cranberries in preventing UTI. The European Association of Urology (EAU) recommends daily consumption of cranberry products, giving a minimum of 36 mg/day proanthocyanidin, at Grade C.[14] Given possible side-effect issues, lack of adequate documentation of dosage, increased calories, and reported problems with gestational diabetes, no recommendation should be given for cranberry-based prophylaxis.

## Prophylaxis with Lactobacilli

Probiotic prophylaxis using the re-establishment of specific strains of lactobacilli which interfere with adherence, growth, and colonisation of uropathogenic bacteria has been suggested to maintain and promote normal flora in the vagina and thus reduce UTI. Studies with different strains have been undertaken (*Lactobacillus casei*, *L. rhamnosus*, *L. crispatus*, *L. reuteri*) with vaginal and oral administration. Data are conflicting but efficacy appears to be weak at best, with results showing little-to-no benefits. Post-antibiotic treatment reduces recurrences in some studies and there are promising results with intravaginal *L. crispatus*, oral *L. rhamnosus* GR-1, and oral *L. reuteri* RC-14.[15–17] In a randomised, double-blind, non inferiority trial of prophylaxis with trimethoprim sulfamethoxazole versus oral capsules containing *L. rhamnosus* GR-1 and *L. reuteri* RC-14, non-inferiority was not proven. However, rates of recurrence and time to reinfection were similar and the increase in resistance seen in the trimethoprim sulfamethoxazole was not reflected in patients treated with lactobacilli.[18] However, current meta-analytic data do not support the efficacy of lactobacilli and, as such, no recommendation for its prophylactic use should be given with a few exceptions.[18]

## Prophylaxis with Oestrogen

Oestrogen replacement in post-menopausal women has been suggested as a possible prophylactic

measure due to putative benefits conferred by restoration of atrophic mucosa and lowering of vaginal pH. The Cochrane Collaboration underwent a meta-analysis of 9 trials of oestrogen prophylaxis (4 oral versus placebo, 3 vaginal versus placebo, and 2 vaginal versus antibiotic) containing 3,345 patients. Prophylaxis with oral oestrogen resulted in no reduction in UTI compared with placebo.[19] Furthermore, there are possible risks of breast cancer, thrombosis, and stroke related to oral oestrogen. Hence, oral oestrogen is not recommended in post-menopausal women to prevent rUTI.

In two of the trials on vaginal oestrogen versus placebo there was a reduction in the number of UTIs (RR 0.25, 95% CI 0.13–0.50 and 0.64, 95% CI 0.47–0.86). However, adverse events were more common in the treated group and included: breast tenderness, vaginal bleeding/spotting, discharge, irritation, burning, and itching. The two studies on vaginal oestrogen versus antibiotic were inconclusive and displayed significant heterogeneity and conflicting results (RR 1.30, 95% CI 1.01–1.68; RR 0.09, 95% CI 0.02–0.36). The authors concluded that vaginal oestrogen may be a valid treatment in patients with significant signs of vaginal atrophy but further studies, perhaps in combination with other therapies, were needed.[19]

## Prophylaxis with Methenamine Salts

Methenamine salts act via the production of formaldehyde from hexamine. Formaldehyde is a bacteriostatic agent which does not appear to be susceptible to acquired resistance.[20] *In vitro* and *in vivo* studies suggest urinary pH <5.5 is needed for bacteriostatic concentrations of free formaldehyde to be generated from methenamine hippurate. Since *Proteus* and *Pseudomonas* strains increase urinary pH, methenamine salts are likely to be ineffective against these organisms.[21]

A meta-analysis of 13 studies of methenamine hippurate containing 2,032 participants found some benefit in patients without urinary tract abnormalities or urinary catheters (symptomatic UTI: RR 0.24, 95% CI 0.07–0.89; bacteriuria: RR 0.56, 95% CI 0.37–0.83). Short-term treatment duration (≤1 week) lead to a reduction in symptomatic UTI (RR 0.14, 95% CI 0.05–0.38) and the rate of adverse events were low.[21]

In 2011, formaldehyde was declared a carcinogenic agent by the National Toxicology Program. Treatment with methenamine salts can lead to high levels of exposure to formaldehyde in the bladder, although any relationship with bladder cancer from use of methenamine is a theoretical risk. However, formaldehyde's carcinogenic effects must be viewed as a limit to its long-term use and, as such, to its usefulness in many settings as a prophylactic. In summary, methenamine hippurate can be taken for 1 week to prevent UTI in patients without urinary tract abnormalities[21] although this is not recommended in the EAU Guidelines.

## Prophylaxis with Vaginal Vaccine

The vaginal vaccine Urovac® is a suppository tablet containing ten heat-killed uropathogenic bacterial species, six serotypes of uropathogenic *E. coli*, alongside *P. vulgaris*, *K. pneumoniae*, *M. morganii*, and *E. faecalis*. Both immune system activation, induction of immunoglobulin G and A, and reduced colonisation of the vagina and bladder have been demonstrated following inoculation. Three trials comprising 220 women have been performed thus far. Trials have assessed either placebo compared with primary immunisation (three vaginal suppositories at weekly intervals) or with primary immunisation and booster (three additional suppositories at monthly intervals).[22–24]

In the initial Phase II trial, there was no difference in the mean number of UTIs over the entire 20-week trial period; 1.4 in both the vaccine and placebo group (p=0.48). However, in participants who withdrew from antibiotic prophylaxis, only 9% in the treatment group had a UTI compared with 47% in the placebo group (p=0.003). Time to first reinfection was longer (13 weeks) in immunised patients compared with control (8.7 weeks) patients, although this was not significant (p=0.45).[22] Similar results were achieved in the two follow-up trials.[23,24] The three available protocols have been conducted by the same research group. Further research in other settings to compare results is needed to ensure proper validation of results.

## Prophylaxis with Immunostimulant OM-89

The immunostimulant OM-89 has been demonstrated to activate both the innate and adaptive immune system in a number of *in vivo*, *in vitro*, and human studies. Six placebo-controlled randomised trials have demonstrated the efficacy of OM-89 in healthy women,[25–30] and efficacy has also been assessed in specific small sub-groups, i.e. post-menopausal women, children, pregnant

women, and spinal cord injury patients;[31–34] three meta-analyses have also been done, all with positive results regarding efficacy and safety.[18,35,36] OM-89 prophylaxis results in a reduction in the number of rUTIs and their symptoms; it also has antibiotic sparing effect, both in the duration of treatment and number of patients requiring treatment, and results in a higher number of disease-free patients, compared with placebo at the end of trials.

### Summary

Evidence for the majority of non-antimicrobial prophylactics is negative or weak; OM-89 is sufficiently documented and it represents an evidence-based alternative to antimicrobial prophylaxis. Consequently, OM-89 currently has the highest grade of recommendation B of non-antimicrobial therapies in the EAU guidelines for the prevention of rUTIs in otherwise healthy women. It is also recommended in other local guidelines including those of Russia and Brazil.[14,37]

## CONCLUSION

In the current medical landscape of increasing bacterial resistance and the high socioeconomic and individual QoL burden, effective prophylaxis against rUTI is essential. The correlation between reduction in UTI episodes and improvement in QoL allows a holistic view of the benefits of prophylaxis which may be helpful in communicating with patients and addressing potential concerns regarding treatment. Currently, OM-89 represents an evidence-based non-antimicrobial prophylaxis recommended with the highest grade in the EAU guidelines for otherwise healthy women and this should be reflected in standards of care.

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