Management of Recurrent Cystitis in Women: Role of the Non-Antimicrobial Prophylaxis

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Alarming Increase of Resistance to Antimicrobial Agents in Pathogens Responsible for Urinary Tract Infections

Prof. Dr. Matteo Bassetti

Fifty years ago there were few, if any, effective antibiotics and there is a growing fear that we are returning to the same situation. The paradox is that the *miracle* drugs (antibiotics) have destroyed the *miracle* (successful treatment of infection). This situation has occurred because over the last 50 years, antibiotics have been overused or misused, and the considerable incidence of illegal over-the-counter sales in the European Union have contributed to this inappropriate use of antibiotics.[1] Thus, bacterial resistance has grown, generating circumstances where almost all antibiotics in the future may be ineffective against today's super bugs.

The difficulty is that resistance is not always reversible and there is a continuing need for new antimicrobial agents which are active against resistant pathogens[2]. Unfortunately companies are not investing in producing new antibiotics and consequently antibiotic options have declined.

The production of new antibiotics has steadily decreased from 16 new antibiotics discovered between 1983 and 1987 to almost none within the last 3 years (Fig.1).[3] A practical solution to moderate the course of this trend is to reduce antibiotic use. Conventional wisdom suggests that this might be achieved by reducing the number of infections, and where antibiotics have to be used, 'use less, less is better' should be the theme. Possible interventions include targeting, improving compliance, restricting prophylaxis to where it is of proven value, continuing education of health care providers and the public, and reduction of excessive use. Less conventional approaches might involve application and better

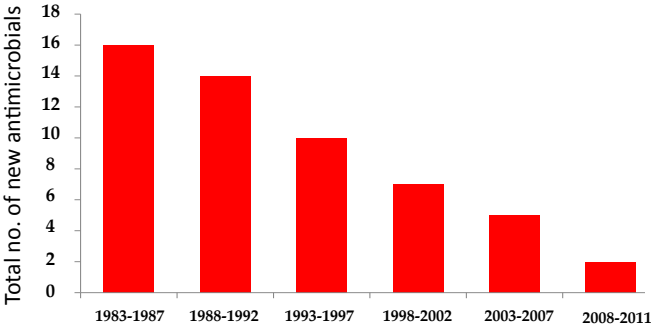

Figure 1. New antibacterial agents approved by the FDA according to the IDSA Public Policy, 2011.

understanding of immunomodulating agents and advances in chronobiology.[4]

The 3 main classes of antimicrobials that can be used to treat urinary tract infection (UTI) are third-generation cephalosporins, fluoroquinolones and carbapenems. 90% of UTI are caused by gram-negative bacteria, usually *E. coli*. Gram-negative bacteria have become increasingly resistant to available antibiotic drugs, limiting the choice of treatment. This is due to extended-spectrum beta-lactamases (ESBLs) - enzymes that are resistant to most beta-lactam antibiotics, including penicillins, cephalosporins and carbapenems (Fig.2). There is a significant incidence globally of ESBL-producing gram-negative bacilli (GNB) such as *E.coli*, *K. pneumonia* and *K. oxytoca* that are resistant to beta lactamases.[5] *E. coli* has been shown to be resistant to cephlosporins and fluoroquinolones leaving the use of carbapenems as the only antimicrobial treatment currently available.[6]

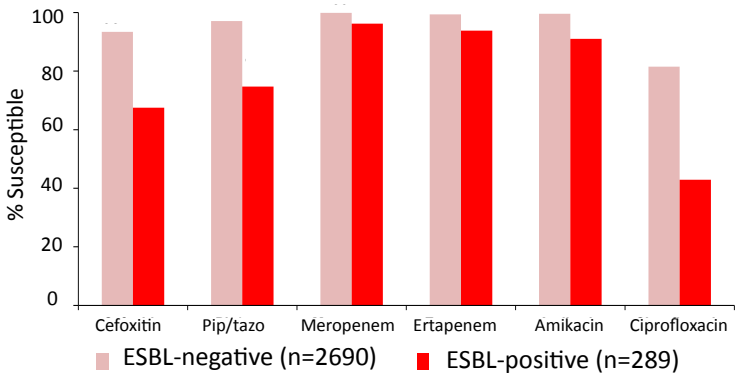

Figure 2. Gram negative bacteria susceptibility to antibiotics: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART)

However, the incidence of carbapenem resistant strains worldwide is increasing. In the past 10 years *Klebsiella pneumoniae* carbapenemase has become widely disseminated, resulting in an increase in carbapenemase-resistant *Enterobacteriaceae* (CRE).[7] CRE produce Verona integron-encoded metallo-β-lactamase and New Delhi metallo-β-lactamase, which are now distributed globally. Metallo-β-lactamases have complex patterns of multi-drug resistance and their spread presents a major health challenge, particularly as mortality rates have increased due to these types of resistant strains.[8,9,10,11,12]

Antibiotic sales in the community represent > 70% of all antibiotic sales. The largest use of antibiotics is for minor respiratory infections (frequently viral) and UTI, which are often self-limiting and self-healing, rendering the usefulness of antibiotics dubious. Antibiotics may be overused as a result of patient demand, and therefore the public should be educated about the nature of infection, the real benefit of antibiotic treatment, and the different solutions that are available to treat minor infections. To counteract the increasing problem of resistance, a multi-factorial strategy (antimicrobial stewardship) is required. This should include benchmarks and education, reduce resistant reservoirs, introduce new drugs and vaccines, and improve diagnostics and infection control.

In conclusion, there is a progressive increase in antibiotic resistance. Infection control measures are useful in delaying resistance, but very rarely capable of reducing the incidence of nosocomial infections involving multi-drug resistant (MDR) organisms. A second antibiotic crisis appears inevitable in the short term because of MDR GNB infections. New therapeutic strategies will likely become available in the next decade. In recurrent UTI, the increasing resistance to many antibiotic families makes it imperative, more than ever, that alternative preventative approaches are used that spare antibiotics.

Prevention of Recurrent Cystitis: Alternative Strategies to Antimicrobials

Dr. Diana Mansour

UTI, mainly cystitis, are among the most prevalent infectious diseases of bacterial origin. Women have a 1 in 3 life time risk of UTI where as men only have a 1 in 20 life time risk, and every year, 5% of women present with frequency and dysuria.[13]

Cystitis is a benign condition but has a detrimental effect on quality of life. Women suffer extensively from pain, discomfort, inconvenience, and disturbance of their daily life. Furthermore, they live with the constant anxiety that they are going to suffer from a new undesirable infection.

Recurrent cystitis is defined as either ≥ 2 acute infections in 6 months or ≥ 3 infections in 12 months.

Recurrent cystitis must be diagnosed by urine culture since relapses or re-infections are frequent in women. 40% of women (980 million) will have a UTI in their lifetime; about 25% of them (245 million) will experience another episode within 6 months, and 44% within 12 months. Therefore, in total about 10% of women suffer from recurrent UTI.[14,15,16]

The most common gram-negative bacterium involved is *E-coli*, which is the cause of around 77% of all UTI (Fig.3).[17] *E-coli* adheres to the uroepithelium, invades very easily, and multiplies quickly causing local inflammation. It is likely that if a person has had one *E-coli* infection they will suffer a recurrence within the following 6 months.[18]

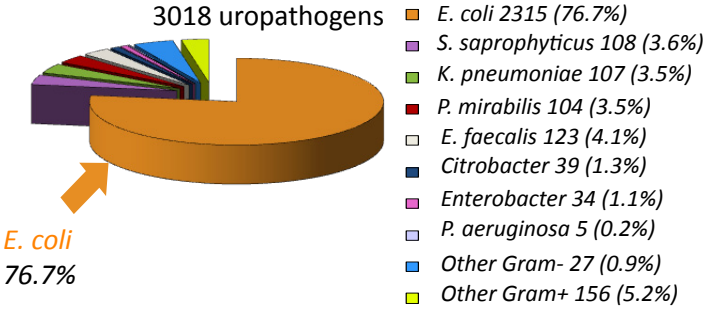

Figure 3. Antimicrobial Resistance Survey on Cystitis (ARESC) on bacterial isolates in patients' urine in Europe and Brazil

To determine and potentially treat a patient who presents with suspected cystitis, the European Association of Urology guidelines (EAU) recommend that the patient must present with 2 of the following 3 clinical symptoms: frequency, dysuria, and/or lower abdominal burning.[19] Routine assessment should also include exclusion of sexually transmitted infection, particularly if there is vaginal discharge, and urinalysis for nitrites and leucocytes. However, the microorganism should only be identified by urine culture in cases of pyelonephritis, recurrent cystitis, and pregnancy, as advised by the European Committee for Antimicrobial Susceptibility.

Antibiotics are an effective treatment for UTI but bacteria can re-establish, causing recurrent cystitis. Whether this is due to persistent bacteria or re-infection is unknown. Treatment of acute infection only is not sufficient. When recurrence is a problem, a long term solution should be considered and prevention taken into account.

Non-antimicrobial measures in the form of lifestyle changes can reduce the risk of recurrent cystitis. If cystitis is related to sexual intercourse, recurrence can be prevented by avoiding the use of diaphragms or spermicide, voiding before and after intercourse and, in post-menopausal women, using a lubricant if they experience vaginal dryness.

The EAU guidelines for non-antimicrobial prophylaxis of UTI suggest considering the use of oestrogens in post-menopausal women, using probiotics (*Lactobacillus sp.*) orally and/or intravaginally, ingesting oral cranberry products and oral/injectable immunoactive prophylaxis.[20]

The rationale for the use of oestrogens in post-menopausal women is that the female genital and lower urinary tract is potentially receptive to the action of oestrogen at all times. This is because the female genital and lower urinary tract is derived from the uro-genital sinus which has oestrogen receptors in the urethra, urethral sphincter, trigone and the muscles of the pelvic floor. Vaginal oestrogen increases the number of vaginal lactobacilli, which reduces the recurrence of UTI. Current evidence shows that topical oestrogen reduces the prevalence of UTI from 23.7% to 6%, reduces sensory bladder symptoms (frequency, urgency, nocturia) from 47.4% to 9.4%, reduces dysuria from 42.2% to 10.7%, improves operative results after prolapse repairs and trans vaginal tape procedures, and may have a synergistic role with α-adrenergic agonists.[21,22,23,24,25] The EAU guidelines give a recommendation Grade C for the use of vaginal oestrogens in post-menopausal women with recurrent cystitis.[26] However, oral oestrogen has been shown to be less effective than topical oestrogen. Four studies involving 2798 women showed that oral oestrogens did not reduce UTI compared with placebo. Oral oestrogen is not as effective because it does not reach all parts of the genital and lower urinary tract.[27]

Depletion of vaginal lactobacilli is associated with UTI risk which suggests, based on the principle of bacterial interference, that repletion may be beneficial. A recent randomised placebo-controlled phase 2 trial using lactobacilli prophylactically following treatment with antibiotics reduced recurrent UTI by 50%.[28] Conversely, a double blind non-inferiority trial comparing trimethoprim-sulfamethoxazole (TMP-SMX) with the lactobacilli *L. Rhamnosus* GR-1 and *L. Reuteri* RC-14 to prevent recurrent cystitis found that after 12 months, the mean number of UTI was 2.9 in the antibiotic group and 3.3 in the lactobacilli group,

showing that *L. rhamnosus* GR-1 and *L. reuteri* RC-14 were inferior in the prevention of UTI compared with TMP-SMX. However, it should be noted that unlike TMP-SMX, the use of lactobacilli did not increase antibiotic resistance.[29] The EAU guidelines for the use of probiotics (2012) state that accessibility of clinically proven probiotics for UTI prophylaxis is not universal. Only *Lactobacillus sp* strains that show benefit should be used for prophylaxis; when commercially available these products can be used once or twice weekly.

Current evidence favours the antibacterial role of cranberry's natural polyphenols or tannins. Cranberries (*Vaccinium macrocarpon*) contain tannin-like compounds called proanthocyanidins (PACs). PACs inhibits P-fimbrial adhesion of *E. coli* to uroepithelial cells. Dosage should be at least 36 mg PAC per day to prevent UTI. There are several products availabe including juices and capsules, but the dosage is not standardised which makes studies difficult to compare.[30,31] Although comparison of studies is difficult, cranberry prophylaxis has been shown to be effective.[32]

Kontiokari *et al* studied women receiving cranberry juice for 6 months, lactobacillus GG drink for 12 months, or no intervention. At the 12 month follow-up point, the difference between the groups was significant (P=0.023 at 6 months, 0.048 at 12 months). Occurrence of UTI was significantly lower in the cranberry group than in the control group (P=0.014 at 6 months, 0.052 at 12 months) showing a 25% recurrence in the cranberry group and 50% in the control group.[33]

Cranberry-containing products have also been shown to prevent UTI in susceptible populations. A systematic review and meta-analysis of 10 trials (1494 subjects) showed that the random-effects pooled risk ratio (RR) for cranberry users versus nonusers was 0.62 (95% CI, 0.49-0.80). Cranberry products were effective in women with recurrent UTI (RR, 0.53; 95% CI, 0.33-0.83), in female populations (RR, 0.49; 95% CI, 0.34-0.73), in children (RR, 0.33; 95% CI, 0.16-0.69), in cranberry juice drinkers (RR, 0.47; 95% CI, 0.30-0.72), and in those taking cranberry-containing products more than twice daily (RR, 0.58; 95% CI, 0.40-0.84). This shows a reduction in UTI in women overall, but is even more effective in women who suffered from recurrent UTI (risk ratio showed 50% reduction).[34]

There are contradictory results concerning the use of cranberries in UTI prophylaxis, however the EAU guidelines (2012), whilst acknowledging the controversy, state that cranberry juice may still be an interesting prophylaxis, and give it a Grade C recommendation. Despite the lack of pharmacological data and the small number of weak clinical studies, evidence suggests that cranberry products are useful in reducing the rate of lower UTI in women, and recommend the daily consumption of cranberry products to be a minimum of 36 mg/day PAC.[35]

If non-antimicrobial measures have been unsuccessful, antibiotic prophylaxis should be considered. This can be continuous antimicrobial therapy, a reduced post-coital dose of antimicrobials, or repeated short-term therapy. Continuous low dose antibiotics are often given, which increase the risk of resistance. Short high dose courses should be given to symptomatic women (or a one off post coital dose) to reduce the chance of a recurrent UTI.

In conclusion, there are several alternative therapies currently available for the prevention of recurrent cystitis that do not increase antibiotic resistance. What is the place of immunoactive prophylaxis?

Immunoactive Prophylaxis in the Management of Recurrent Cystitis

Prof. Dr. Harald Meden

Antibiotic resistance is causing a serious problem in the treatment of recurrent cystitis. The European Guidelines on Urological infection (EAU) recommend that the treatment of recurrent cystitis adheres to the following principles: initially general prophylaxis should be considered; followed by non-antimicrobial prevention (in order to avoid antibiotic use); finally, if non-antimicrobials have been unsuccessful, antimicrobial prevention should be used.[36]

In line with the EAU guidelines, immunoactive prophylaxis is a non-antimicrobial option that should be considered in the management of recurrent cystitis. Recurrences of infection or chronic infections can be triggered by any reduction in the efficiency of the host's immune response, e.g. environmental factors, overuse of antibiotics, age or genetic factors. Therefore, the patient's underlying immune status

is fundamental in the development of recurrent urinary tract infections (UTI). Any intervention aimed at enhancing the immune system and the host's defences in the urinary tract represents an excellent opportunity for preventive medicine.[37]

The immune system can also be stimulated to target the urinary tract. Uropathogenic *E. coli* can be one of thousands of different clones or strains. There are two immunoactive strategies that can be used to target *E. coli*, a single antigen (e.g. Type 1 fimbriae) or several antigens (e.g. extract of inactivated uro-pathogens). A mixture of oral antigens can stimulate the immune system in the urinary tract as activated cells and antibodies in the mucosa associated lymphoid tissue (MALT) in the gut can re-circulate to other MALT via the systemic blood circulation or the lymphatic system where they act as a mechanism of defence against uro-pathogens (Fig.4). OM-89 (Uro-Vaxom®) is an oral immunoactive product manufactured from 18 selected and standardised strains of *E. coli* known to be the most common uropathogens responsible for cystitis.

OM-89's biological activity has been demonstrated in several pre-clinical *in vitro* and *in vivo* studies specifically in the urinary tract.[38,39,40,41,42,43] Furthermore, its clinical efficacy and safety has been tested in five randomised double blind placebo controlled clinical studies of 6 months' duration and confirmed by other long-term studies (12 months duration) and a meta-analysis.[44,45,46,47,48]

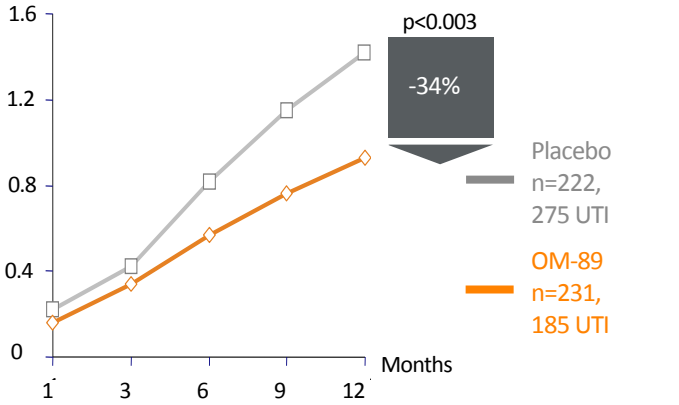

Figure 5. Cumulative relapse rate of UTI by visit (ITT population; p<0.003)

OM-89 has been shown to reduce the mean number of UTI compared with placebo by up to 50% in several studies and has been shown to have an antibiotic sparing effect with a reduction in mean number of days of antibiotic intake of up to 67%.[49] In a multicentre randomised placebo controlled trial (12 months' duration), 453 women suffering from recurrent cystitis were given OM-89 once daily for 3 months, and following 3 months' observation were given a booster regimen for a further 3 months. The cumulative mean rate of UTI was reduced in the OM-89 group by 34% (statistically significant) compared with placebo at the end of the study (Fig.5).[50] A meta-analysis of 5 double blind placebo controlled studies pooled data from approximately 1000 patients suffering from recurrent UTI. The analysis showed that OM-89 (*verum*) reduced the mean number of UTI by 36% compared with placebo at 6

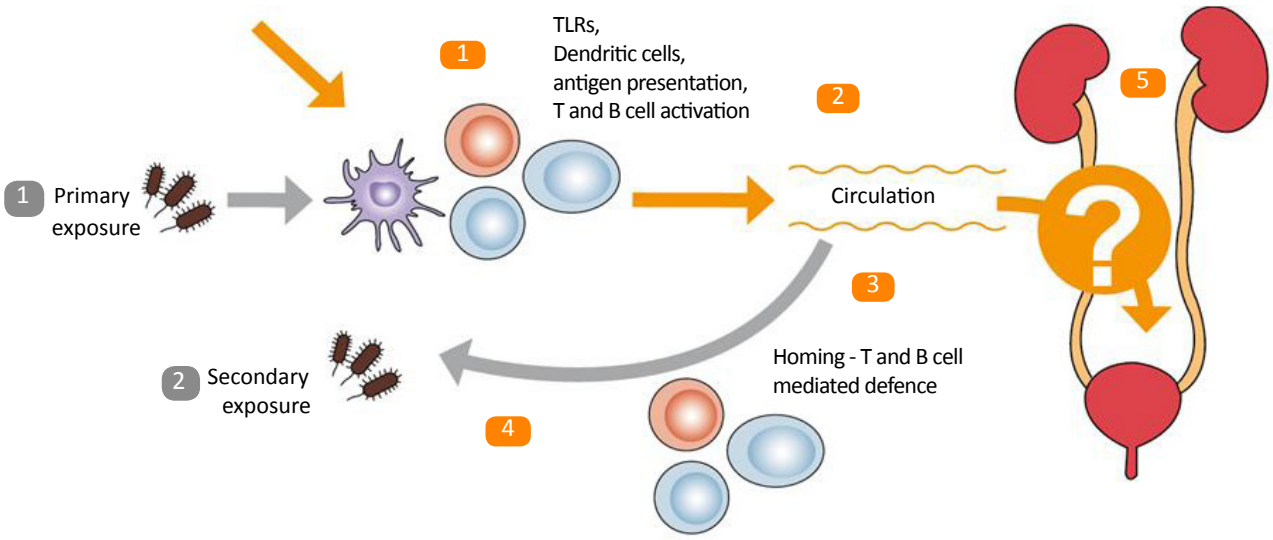

Figure 4. Hypothesis of activation of immune system effectors in the Mucosa Associated Lymphoid Tissue (MALT) in the gut and the bladder via systemic re-circulation, after oral ingestion of antigens entering OM-89 composition

months and by 39% at the end of all studies (including 12 months' data: Bauer *et al*. data not shown) (Fig.6). Furthermore, the same analysis showed that studies with the largest number of UTI in the placebo group where those that demonstrated the largest benefit from OM-89 prophylaxis. This suggests that the higher the risk of bladder infections, the greater the benefit of prophylaxis with OM-89. The distribution of post baseline UTI per patient was in favour of OM-89 and this was statistically significant (Fig.7). The clinical effect was associated with a significant reduction of antibacterial use (data not shown); the meta analysis showed that OM-89 was well tolerated with a safety profile comparable with placebo.[51]

OM-89 has also been tested in special target populations. Pilot studies have been conducted in children, post-menopausal women, pregnancy, and patients with spinal cord injury. The results have shown OM-89 to have a good safety profile[52] in these special populations compared with baseline values. In particular, in pregnant women the incidence of UTI was reduced by 62% compared with baseline values, only 3.2% of patients included in the study experienced slight side effects of nausea and heartburn, though the authors believed that this was possibly associated with pregnancy, and all new-born infants were born alive and healthy with normal Apgar scores.[53]

In children UTI were reduced by 70%; in post-menopausal women the reduction was 65% compared with baseline values. In a randomised cross-over study versus placebo in paraplegic patients there was a 50% reduction in mean bacteriuria over a 6 month period.[54,55,56,57]

Recurrent UTI can have a detrimental effect on the patient's quality of life. The Harmony study involving 575 patients showed that at entry 62% of patients presented with a global Hospital Anxiety and Depression Scale (HAD) score indicative of minor anxiety or depression. At the end of the survey, a 59% decrease in mean lower UTI was observed, along with a 36% decrease in anxiety state, 25% decrease in depression score and a decrease of 32% in overall HAD scores, all of which were highly significant ($p<0.0001$) compared with baseline. These improvements in quality of life indicators significantly correlated ($p<0.0001$) with the reduction in cystitis (Table 1). [58]

Recurrent cystitis is common and is a real burden for women, who experience unbearable pain and the anxiety of further cystitis. Treating repeated acute infections alone is suboptimal in providing relief for these patients, and does not assure successful disease management, causing women to continue returning for treatment. In order to

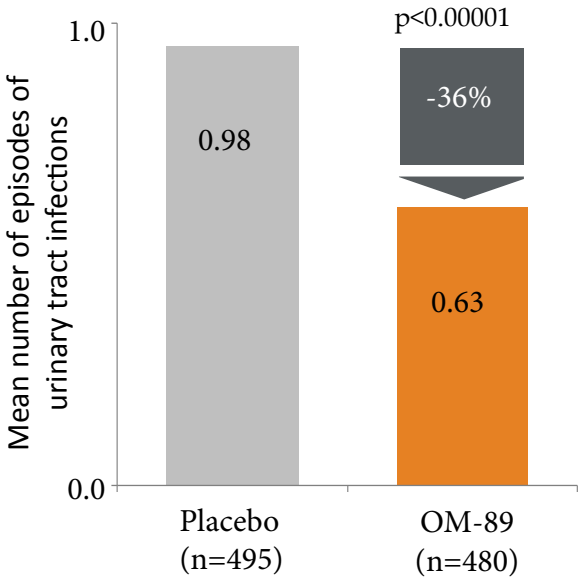

Figure 6. Mean number of UTI at 6-months in OM-89 and placebo groups (test for heterogeneity, p=0,002; test for overall effects, p<0,00001)

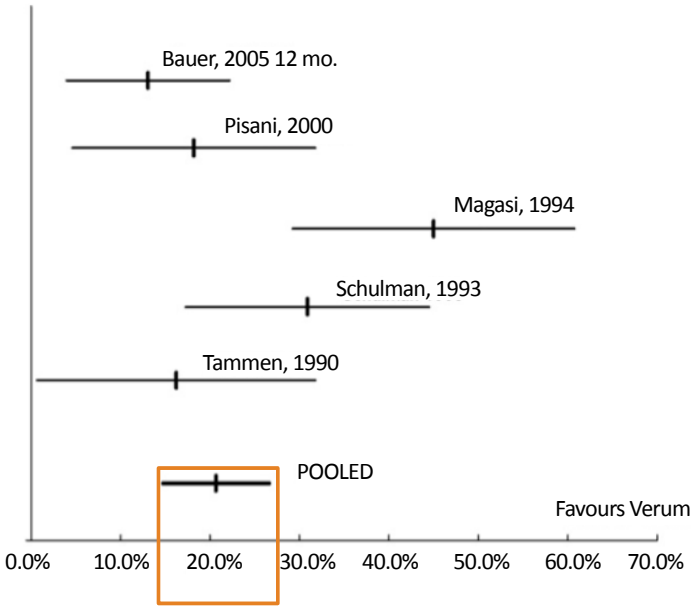

Figure 7. Percentage of patients without urinary tract infections: difference between OM-89 and placebo at the end of the studies

Correlations	Day 0		Day 180	
	Number of UTI Mean (Std Dev)	Coefficient of correlation (p value)	Number of UTI Mean (Std Dev)	Coefficient of correlation (p value)
Depression score and number of urinary episodes	2.8 (1.2)[1]	coeff= 0.14027 (p=0.0023)	1.6 (1.2)[1]	coeff= 0.28136 p<0.0001
Anxiety score and number of urinary episodes	2.7 (1.3)[2]	coeff= -0.02349 (p=0.6081)	1.5 (1.3)[2]	coeff= 0.29786 p<0.0001
Global HAD score and number of urinary episodes	2.7 (1.3)[3]	coeff= 0.06010 (p=0.1934)	1.1 (1.1)[3]	coeff= 0.32234 p<0.0001

Key: coeff=coefficient of correlation; Std Dev=standard deviation; UTI=urinary tract infection

1. Number of UTI for patients with a depression score ≥ 8 at baseline
2. Number of UTI for patients with an anxiety score ≥ 8 at baseline
3. Number of UTI for patients with depression and anxiety scores < 8 at baseline were excluded

Table 1. Correlation between anxiety and depression scores and UTI number at Day 0 and Day 180

improve treatment outcomes and patients' quality of life, an effective preventative treatment, validated by evidence-based medicine, is required. Several strategies are available to prevent recurrent bladder infections, including antimicrobial prophylaxis. The alarming increase in antibiotic resistance and the poor armamentarium against gram-negative bacteria necessitate alternatives to antibiotics.

OM-89 is such an alternative. It has been shown to be more effective than placebo in several randomised trials and meta-analysis. Furthermore, it is recommended in the EAU guidelines for immunoprophylaxis in women with recurrent cystitis with the highest grade of recommendation (Grade B) and the top level of scientific evidence (1a).

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