Recurrent Uncomplicated Urinary Tract Infections

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Abstract

Recurrent uncomplicated urinary tract infections (rUTIs) are very common and impose a substantial disease burden. Acute episodes can be successfully treated with antibiotics but recurrence occurs in about 20–30 % of adult women within 3–4 months. Historically, antibiotics have been used as prophylaxis against rUTIs but the rise in antibiotic resistance has led to the search for alternative strategies. Such strategies include the use of probiotics and oestradiol, use of immunoactive products and use of plant extracts such as cranberry products, although data to support the efficacy of the latter are inconclusive. The immunoprophylaxis approach involves oral treatment with an extract from 18 uropathogenic strains of *Escherichia coli* (OM-89, Uro-Vaxom®). OM-89 stimulates the innate and adaptive immune responses against UTI pathogens. Its efficacy and safety has been proven in several clinical trials. Recent guidelines published by the European Association of Urology (EAU) recommend the use of these alternative approaches, in particular OM-89, to prevent recurrence of rUTIs.

Keywords

Recurrent urinary tract infection, antibiotic resistance, treatment guidelines

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Bacterial Resistance and Safety Issues in Urinary Tract Infection Management and Prevention

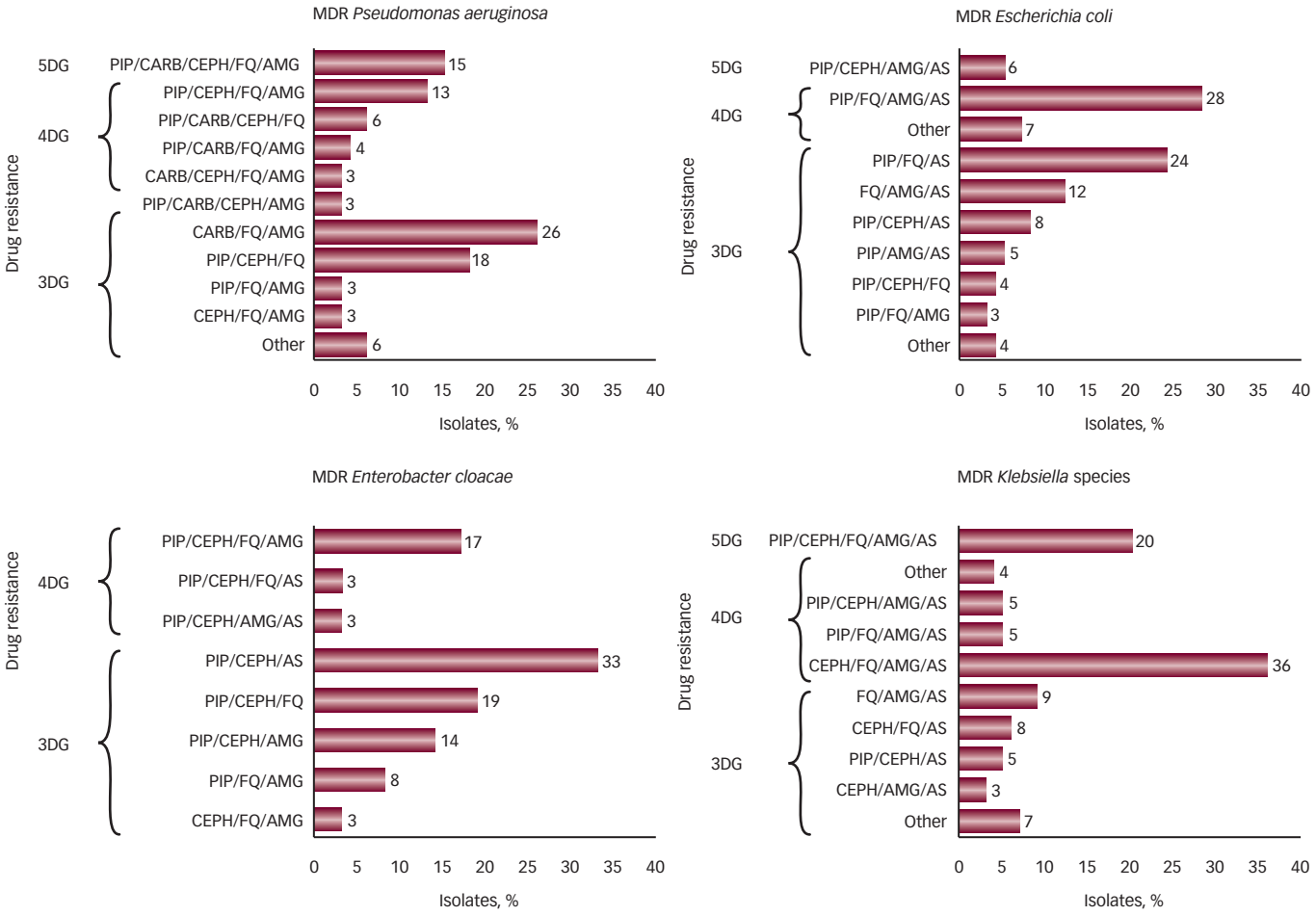
Javier Garau

The increasing prevalence of antibiotic resistance is becoming a worldwide health problem, in both the hospital setting and in the community. Infections with new multi-drug-resistant (MDR) bacterial species are becoming more difficult to treat. Pan-resistant strains now exist in several microbial species. Infections due to MDR organisms have led to a substantial increase in morbidity and death. If this trend does not change, there will be a progressive increase in the number of potentially untreatable bacterial infections.

The increasing prevalence of MDR Gram-negative bacteria (GNB), including scherichia, between 1998 and 2003 was illustrated in a recent study (*see Figure 1*).[1] *Escherichia coli* is the leading cause of community-onset bacteraemia in seniors with an overall rate of 150 cases per 100,000 person-years, approximately three-times higher than the rate of pneumococcal bacteraemia.[2] In a study of outpatients having recent contact with the healthcare system, *E. coli* was found to be the most common cause of healthcare-associated bloodstream infections.[3] Also, in a population-based study of UTIs caused by GNB, *E. coli* was the most common pathogen, being detected in 74.9 % of cases.[4] The mechanism of resistance in GNB is illustrated in *Figure 2*.[5]

GNB-associated problems that include the production of extended-spectrum β-lactamases (ESBL) are a major concern. The production of ESBL has become a global problem and a considerable body of published data demonstrates their increasing prevalence in GNBs, particularly in *E. coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*, all of which are significant causes of UTIs.[6–12] Foreign travel is a significant risk factor for developing community-onset ESBL-producing *E. coli* gut colonisation, with the

Figure 1: Percentage of Isolates of Multidrug-resistant Gram-negative Bacteria Recovered Within the First 48 Hours After Admission to the Hospital, by Species



3DG = 3-drug resistance group; 4DG = 4-drug resistance group; 5DG = 5-drug resistance group; AMG = aminoglycosides; AS = ampicillin/sulbactam; CARB = carbapenems; CEPH = ceftazidime or cefepime; FQ = fluoroquinolones; MDR = multi-drug-resistant; PIP = piperacillins. Source: Pop-Vicas and D'Agata, 2005.[1]

highest risk in trips, including medical tourism, to India, the Middle East and Africa.[13] Colonised individuals bring these organisms back to their countries and explain the dissemination and infection caused by these strains in many parts of the world. In a recent study, Turkey, Greece and Portugal tended to have higher resistance among *E. coli*, while Lithuania, Estonia and France tended to have less resistance.[14]

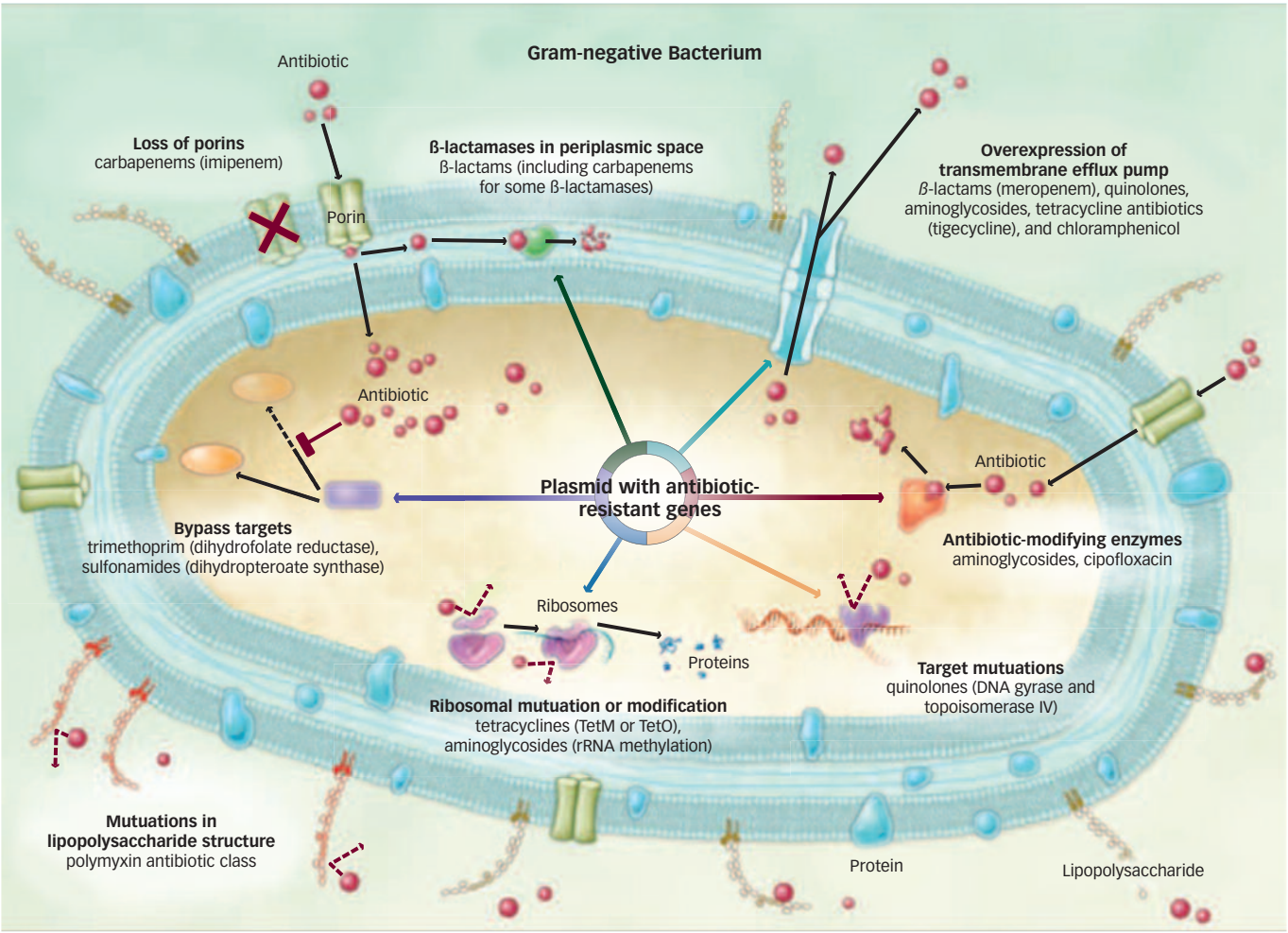
Although there is considerable regional variation, GNB resistance appears to be a worldwide phenomenon. Clinical experience shows that *E. coli* strains isolated from UTIs are becoming increasingly resistant to many antibiotics. The treatment of these infections with oral agents is severely compromised and very few agents are available, such as fosfomycin and nitrofurantoin. Among ESBL-producing *E. coli* UTIs, the increased exposure to fosfomycin has resulted in a rise in fosfomycin resistance in Spain.[15] By contrast, a recent Swedish study (Upsala community) identified a low frequency of antibiotic resistance among urine isolates of *E. coli* in the community, despite a major hospital outbreak with *K. pneumoniae* producing ESBL.[16]

The threat posed by carbapenemase-producing strains of *Enterobacteriaceae* that cause UTIs is considerable. These bacteria are often resistant to all β-lactam antibiotics and are frequently co-resistant to most other antibiotics, leaving few treatment options. The first case of carbapenemase production in *Enterobacter cloacae* was reported in 1993.[17] Since then, many carbapenemases have been identified in *Enterobacteriaceae*, belonging to three classes of β-lactamases A, B and D.[18] As of July 2010, healthcare-associated carbapenemase-producing *Enterobacteriaceae* have been reported in most European countries and are endemic in Greece and Israel.[19]

Gram-negative *Enterobacteriaceae* with resistance to carbapenems conferred by New Delhi metallo-β-lactamase 1 (NDM-1) represent the latest threat. The *bla*NDM-1 gene is present on plasmids thus is easily transferred. It is widespread in India and Pakistan. Many patients in the UK infected with NDM-1-producing bacteria had recently travelled to India for medical procedures.[20] Patients infected with NDM-1-producing *Enterobacteriaceae* have now been reported worldwide.[21] NDM-1 is frequently acquired by *E. coli* strains and has been identified in *E. coli* ST-type 131 as a source of community-acquired infection.[22] This strain is responsible for the worldwide dissemination of extended spectrum β-lactamases around the world.[23] *E. coli* is the most common cause of diarrhoea in children in India and may therefore increase the risk of drug-resistant strains being released into the environment and further spread among humans. This was illustrated by a recent study that found NDM-1-producing bacteria were prevalent in tap and environmental water in New Delhi.[24]

In conclusion, there has been a progressive increase in antibiotic resistance in most bacterial species of human interest. Infection

Figure 2: Mechanisms of Resistance in Gram-negative Bacteria and the Antibiotics Affected



Seven mechanisms of resistance are shown in the Gram-negative bacterium, with some being mediated by a mobile plasmid. These mechanisms include the loss of porins, which reduces the movement of drug through the cell membrane; the presence of β-lactamases in the periplasmic space, which degrades the β-lactam; increased expression of the transmembrane efflux pump, which expels the drug from the bacterium before it can have an effect; the presence of antibiotic-modifying enzymes, which make the antibiotic incapable of interacting with its target; target site mutations, which prevent the antibiotic from binding to its site of action; ribosomal mutations or modifications, which prevent the antibiotic from binding and inhibiting protein synthesis; metabolic bypass mechanisms, which use an alternative resistant enzyme to bypass the inhibitory effect of the antibiotic; and a mutation in the lipopolysaccharide, which renders the polymyxin class of antibiotics unable to bind the target. Red spheres indicate antibiotics. Source: Peleg & Hooper, 2010.[5]

control measures are useful in delaying resistance but are rarely capable of reducing the incidence of MDR organisms. A second antibiotic crisis appears to be inevitable in the short term in MDR GNB infections. New therapeutic strategies currently in development are unlikely to become available for at least 3–5 years. In the field of UTIs, the increasing resistance to many classes of antibiotics makes prophylaxis with alternatives to antimicrobials imperative. ■

The European Association of Urology Guidelines Offer More than Antibioprophylaxis to Manage Recurrent Urinary Tract Infections

Kurt G Naber

Data on the prevalence of recurrent uncomplicated urinary tract infections (rUTIs), which is defined as three or more UTIs per year (European Association of Urology [EAU] Guidelines) was discussed. In sexually active women, up to 75–90 % of acute UTI episodes may be intercourse-related[25,26] and strongly associated with the frequency of intercourse and the use of diaphragms and spermicide.[27] At present, the treatment of acute episodes of cystitis is not difficult; the treatment aims to achieve rapid disappearance of symptoms. The pathogen responsible for UTIs is *E. coli* in 70–90 % of cases, the remainder being caused by bacteria such as *Staphylococcus saprophyticus*, *Klebsiella* species and *P. mirabilis*. According to the current EAU guidelines the first-line treatments are fosfomycin,

trometamol, pivmecillinam and nitrofurantoin. Trimethoprim and fluoroquinolones may also be used although resistance to these antibiotics in *E. coli* and the collateral damage of fluoroquinolones should be taken into account.

In cases of rUTIs, however, acute treatment is insufficient and the likelihood of recurrences must be addressed. Within 3–4 months, 20–30 % of women will have a recurrence and 10–20 % of women will have rUTIs at some point in their lives.[28,29] Several risk factors affect susceptibility to rUTIs; these are summarised in *Table 1*. The routine approach to prophylaxis of rUTIs has involved daily or weekly reduced doses of antimicrobials, post-coital reduced doses of antimicrobials and self short-term therapy.

A Cochrane review found a 12.3 % recurrence rate of UTIs following antibiotic prophylaxis and a 65.5 % recurrence rate with placebo.[28,30] However, these figures are based on old data and there have not been many recent studies on antibiotic efficacy in prevention. Increased resistance and new safety concerns such as hepatic and pulmonary rare but severe events associated with nitrofurantoin long-term use have limited the options for antibiotics. Current EAU guidelines state that antimicrobial prophylaxis for rUTIs should be considered only after counselling and behavioural modifications have been attempted and in women for whom non-antimicrobial measures have been unsuccessful.[31] There is clearly a need for alternative strategies in the prevention of rUTIs.

Table 1: Factors Affecting Susceptibility to Recurrent Uncomplicated Urinary Tract Infections

Biological	Behavioural	Urogenital
Prior history of UTIs	Sexual intercourse	Incontinence
Diabetes mellitus	Diaphragm and spermicide usage	Urinary obstruction
Oestrogen deficiency, particularly in post-menopausal women	Recent antibiotic use	Sphincter detrusor dyssynergia
		Urological surgery

UTIs = urinary tract infections.

Different approaches to managing rUTIs including bacterial interference with probiotics and local hormone replacement therapy, immunoprophylaxis with OM-89, urine acidification and endothelial adherence suppression using cranberry juice do exist and should be used appropriately. ■

Alternative Strategies in the European Association of Urology Guidelines for the Prophylaxis of Uncomplicated Cystitis – A Rationale

Björn Wullt

The problem of MDR bacteria has prompted the need for alternative prophylactic strategies for various infections including UTIs. Three main approaches are recommended in the EAU 2011 guidelines:[31] the bacterial interference approach including local oestrogen supply, the use of bacterial adherence suppression by extracts from the plant *Vaccinium macrocarpon* (or cranberry) and the immunoprophylaxis approach.

The rationale for the bacterial interference approach is that the growth of one bacterial strain or species protects against superinfection. This concept has found several clinical applications in UTIs. In asymptomatic bacteriuria *E. coli* strain 83972 has a protective effect in patients with neurogenic bladders and rUTIs.[32] In addition, the intravaginal administration of oestriol has been shown to prevent rUTIs in post-menopausal women by increasing vaginal colonisation by *Lactobacillus*.[33] In a recent study, 100 young women with a history of rUTI were randomised to receive either intravaginal *Lactobacillus crispatus* (Lactin-V) or placebo. The treatment group showed a reduction of almost 50 % in recurrence rate compared with placebo.[34]

The bacterial interference approach, which includes local oestrogen supply in post-menopausal women, is recommended in the latest EAU guidelines. However, local treatment with lactobacilli strains for prophylaxis of UTI is only recommended with strains that have been clinically proven. *L. crispatus* is currently not available outside the US but, once available, this product may be used in clinical practice.

Plant extracts, in particular cranberry juice, are popular treatments for UTI. *In vitro* data show that cranberries contain a tannin called proanthocyanidin (PAC), which inhibits P-fimbrial adhesion of *E. coli* to uro-epithelial cells on the bladder wall. Several products are available, including capsules and juices. However, the lack of standardised doses makes study results difficult to compare. In an open study from 2001, 150 women with rUTIs were randomly allocated into three groups and were given cranberry juice concentrate, a *Lactobacillus* drink or no intervention. At a six-month follow up, there was a 16 % recurrence of UTIs in the cranberry group compared with 36 % in the control group, corresponding to a 50 % reduction.[35] A Cochrane review conducted in 2004 concluded that there is some evidence that cranberry juice may decrease the number of UTIs over a 12-month period in women.[36] The EAU guidelines from 2011 consequently stated that evidence does exist for the use of cranberry in reducing the rate of UTIs. The recommended dosage is at least 36 mg PAC per day.

Since the publication of the 2011 EAU guidelines, conflicting data on cranberry juice effectiveness have been produced. In a recent double-blind, placebo-controlled study among 319 young women

who presented with an acute UTI, the consumption of cranberry juice twice daily did not result in a significant risk reduction in UTIs compared with placebo.[37] In this study the PAC content was defined but too few recurrences were recorded in both groups (overall 16.9 % in both groups compared with an expected 30.0 %) to produce reliable statistical power. In another double-blind study, 221 pre-menopausal women with rUTIs were randomised to 12-month use of trimethoprim-sulfamethoxazole (TMP-SMX) or cranberry capsules of defined PAC content. After 12 months of follow-up, the cranberry capsules were found to be inferior to TMP-SMX.[38] In the coming update of the EAU guidelines these studies will be reviewed and the level of recommendation for cranberry juice may be changed.

A different concept in the management of recurrent UTIs is immunoprophylaxis. Defence against bacterial infection in the urinary tract should require full functioning of the innate immune system, but the role of adaptive immunity in UTI remains to be defined. Innate defences provided by the mucosal barrier can be maintained by urinary flow and regular complete emptying of the bladder. Innate immunity is triggered by bacterial pattern antigens (pathogen-associated molecular patterns [PAMPs]) that are recognised by pattern recognition receptors (PRRs). In the human urinary tract, the PRRs are Toll-like receptors (TLRs). Dysfunctions in TLRs have been linked to asymptomatic bacteriuria (ABU) in children.[39] Furthermore, the level of TLR response to a bacterial challenge in the urinary tract varies with each individual and is directly influenced by host genetics.[40]

The biggest challenge in the development of immunoprophylactic agents is the choice of an antigen, since uropathogenic *E. coli* consists of thousands of different clones. Single antigen approaches include type 1 fimbriae[41] or iron uptake receptors,[42] but were abandoned because they did not work. An alternative approach employed several antigens, leading to the development and manufacturing of OM-89 (Uro-Vaxom®), a type of peroral vaccine (uro-prophylaxis) comprising an extract of 18 uropathogenic *E. coli* strains.

The effect of immunoprophylaxis can be studied by using molecular biomarkers and by clinical efficacy. Several experimental and laboratory studies have demonstrated the effects exerted by OM-89. Studies in experimental and animal models have shown that OM-89 stimulates innate immunity by increasing neutrophils and macrophage phagocytosis[43] and, via the upregulation of dendritic cells,[44] it stimulates specific immunity with activation of T and B cells.[44,45] Serum IgA and IgG levels against all 18 *E. coli* antigens were substantially raised compared with controls[45] and sIgA levels were slightly increased in human urine.[46]

The product has also been shown to have anti-inflammatory properties in the urinary tract in mice.[47] In terms of clinical efficacy, OM-89 has demonstrated UTI recurrence reductions of 30–50 % in several studies, described in detail below. As a result of the experimental and clinical data, OM-89 has been recommended in the EAU 2011 guidelines for the treatment of UTIs.

In summary, the EAU guidelines are likely to continue to recommend the use of bacterial interference strategies (local supply of oestrogens and *L. crispatus* [Grade C]) and immunoactive therapy (OM-89 [Grade B]) in the prevention of recurrent UTIs. The future for cranberry juice in terms of recommendation grade is less certain. ■

Immunotherapy with OM-89 Reduces Urinary Tract Infection Recurrence and the Need for Antibiotics – Clinical Evidence and Consequences in Daily Practice

Kurt G Naber

Immunotherapy with OM-89 has been extensively studied. Five randomised controlled trials (RCTs) in otherwise healthy adults suffering from rUTIs have provided evidence of the clinical efficacy and safety of OM-89 over six months; the results are summarised in *Figure 3*.

In the most recent six-month, randomised, multicentre, double-blind, placebo-controlled study, 166 patients suffering from rUTIs were given one capsule daily of either OM-89 or matching placebo over a period of three months and assessed after a further three months after drug administration had ended. OM-89 significantly reduced the number of recurrences by 50 % compared with placebo and antibiotic consumption (frequency of prescriptions) was reduced by 67 %.[48]

The Prevention of Infection Recurrence by *E. coli* in the Urinary System (PIREUS) study enrolled 453 women aged 18–65 with ≥3 acute UTIs in the previous year. UTI was defined as two or three symptoms for at least two days with positive results in microbiological urine analysis (>10^3 cfu/ml). Patients received OM-89 or matching placebo; one capsule per day for 90 days, three months without treatment, then a booster of one capsule/day for the first 10 days in months seven, eight and nine and they were followed up at 12 months. OM-89 significantly reduced the incidence of UTIs by 34 %. At the end of the study, the distribution of post-baseline UTIs was in favour of OM-89 and 55 % of OM-89 treated patients had experienced no recurrences. In parallel, the consumption (mean days of intake) of anti-infective medications had decreased by 13 % compared with placebo.[47]

A meta-analysis of five randomised placebo-controlled studies (including Bauer,[49] 12-month study) found that after six months of treatment with OM-89 the number of UTIs was reduced by 36 % versus placebo (39 % at the end of the studies regardless of the study duration), and the number of patients free of UTIs was 20 % lower versus placebo. Furthermore, studies that showed the largest number of rUTIs with placebo treatment showed the largest reduction of rUTIs with OM-89 treatment. In patients treated

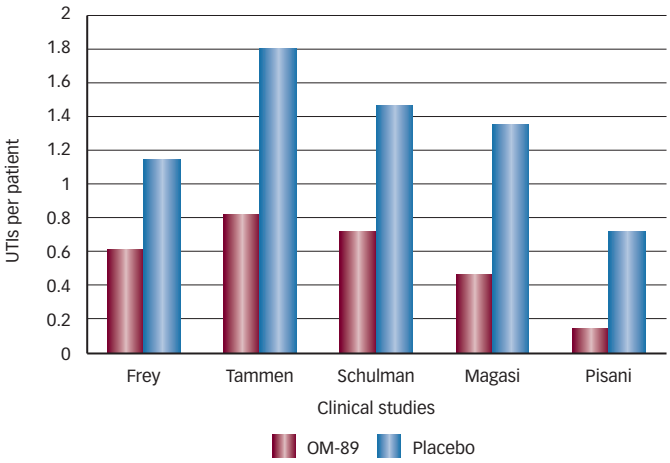
with OM-89, the overall consumption of antibiotics was significantly reduced.[50] It can be concluded that OM-89 gave a significant reduction in UTI recurrences, reduced antibiotic consumption and this effect was associated with an improvement in signs and symptoms of UTIs (such as dysuria). OM-89 showed a good safety profile.

The administration of OM-89 has also been studied in pregnant women. In an open pilot study involving 62 pregnant women with bacteriuria, patients were given one capsule a day of OM-89 at the time of infection and they were followed up for 3–6 months until delivery. The result was a significant reduction in dysuria[51] and all newborns were healthy with a normal Apgar score.

Another potentially useful application of OM-89 is in post-menopausal women who are at high risk of rUTIs because uropathogens can easily colonise the urogenital mucosa as a result of oestrogen deficiency. In an observational study of 55 post-menopausal women over a 12-month period (six months without and six months with OM-89 treatment), there was a 65 % reduction in the rate of UTIs over six months of OM-89 treatment.[52] An RCT investigating the effects of OM-89 treatment in this older age group would be valuable.

In conclusion, a significant number of women suffer from rUTIs that impose a social and economic burden. Therefore, there is a need for prophylaxis to avoid the need of repeated cycles of antibiotics to treat acute re-infections. Few antibiotics are suitable for prophylaxis of UTIs due to side effects or problems caused by MDR uropathogens. Also, the lack of new antibiotics for UTIs raised the urgent need for effective alternative strategies. OM-89 is currently the prophylactic agent for which the best clinical evidence exists, supporting its use in the prevention of rUTIs, that is recommended with Grade B by the EAU guidelines and mentioned in other guidelines or recommendations on urological infections worldwide such as in Brazil and Russia. ■

Figure 3: Clinical Studies of OM-89 Showing Reduction of Urinary Tract Infections



UTIs = urinary tract infections. Source: Naber 2012.[53]

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