EMJ EUROPEAN MEDICAL JOURNAL

UROLOGY

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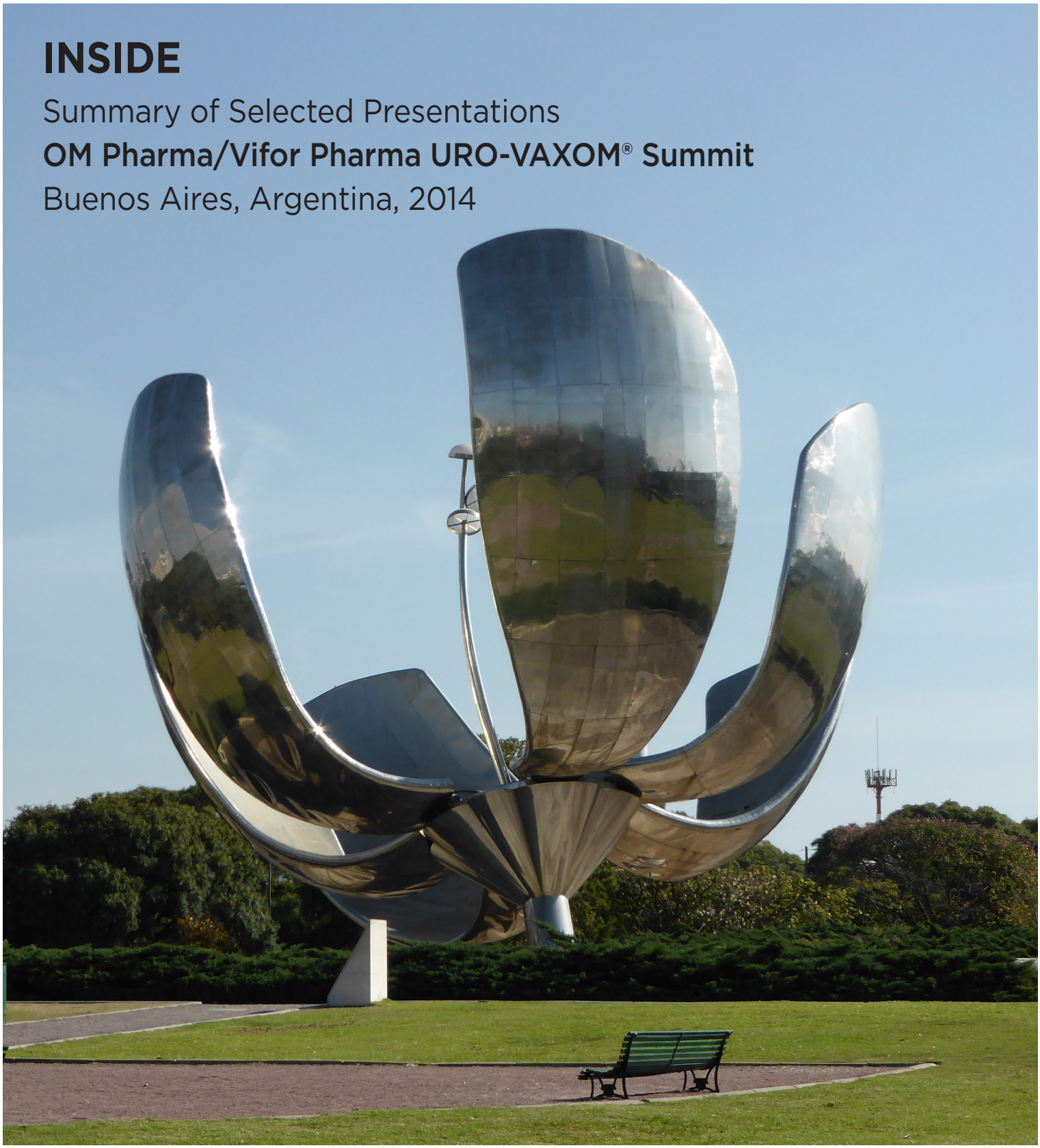
INSIDE

Summary of Selected Presentations

OM Pharma/Vifor Pharma URO-VAXOM® Summit

Buenos Aires, Argentina, 2014



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RECURRENT URINARY TRACT INFECTIONS: ANTIBIOTIC RESISTANCE AND GUIDELINES

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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Disclosure: The authors are global consultants of OM/Vifor Pharma Company, Meyrin, Switzerland.
Acknowledgements: Assistance was provided by Ewen Legg, ApotheCom ScopeMedical.
Support: The publication of this article was funded by OM/Vifor Pharma. The views and opinions expressed are those of the authors and not necessarily those of OM/Vifor Pharma.
Citation: EMJ Urol. 2014;1(Suppl 2):3-13.

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.

The emergence and spread of antibiotic resistance (ABR) is a critical issue for global health and wellbeing. Due to its prevalence and empiric treatment with antibiotics, infection of the urinary tract represents one of the primary fronts in the battle against drug-resistant organisms. An understanding of the prevalence of uropathogens, their ABR, and effective guidelines based on this knowledge will be key in combating this global health threat.

THE EMERGENCE AND SPREAD OF ABR

Alexander Fleming's serendipitous 1928 discovery of the antimicrobial action of penicillin and its isolation and therapeutic use was the beginning of a process. However, this process was not to lead, as infamously asserted by Dr William H. Stewart, US Surgeon General in the latter half of the 1960s, to closing the book on infectious disease. Rather the process has been a cyclical one whereby antibiotics, once rightly hailed as miracle drugs, are driving antimicrobial resistance (AMR) and, thus, are destroying their own miracle.[1] The deterioration in antibiotic efficacy threatens a return to the medical landscape of 50 years ago when few, if any, effective antimicrobial agents existed.[2]

Emergence and Mechanisms of Resistance

AMR occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs, chemicals, or other agents designed to cure or prevent infections.[3] The process of antibiotic-induced resistance begins when exposure of a sensitive microbial population to an antibiotic leads to selection of resistant clones. This is followed

by expansion of these clones which can, in turn, lead to an outbreak, an epidemic, or a pandemic. Imprudent use due to profligate prescribing practices and over-the-counter sales[4] make the development of resistant strains much more likely. Once established, this resistance may not be reversible, necessitating the need for new antimicrobial agents or control strategies.[5] Despite this, the approval rate of new agents by the US FDA dropped by almost 90% between 1983–2011, with only two new agents approved between 2008 and 2011.[6]

All the major classes of antibiotics are now affected by at least one resistance mechanism (Table 1). There are three major classes of mechanism through which bacteria become resistant to antibiotics: structural modification of the antibiotic target site, resulting in reduced antibiotic binding or formation of a new metabolic pathway preventing metabolism of the antibiotic; altered uptake of antibiotics, resulting in decreased permeability of the bacterial cell wall or increased efflux; and antibiotic inactivation through acquisition of genes encoding enzymes that inactivate antibiotics. One of the most important mechanisms of resistance for uropathogens is the production of β-lactamase enzymes. The evolutionary process behind β-lactamase production and modification also illustrates the adaptation of resistance mechanisms caused by the selective pressure of successive generations of antibiotics on bacterial reproduction.

β-lactam antibiotics work by inhibition of bacterial wall formation, and comprised 65% of the world market for antibiotics in 2003.[8] The introduction of the first β-lactam antibiotic, penicillin (acting on wild-type bacteria), led to the expression of the first β-lactamase enzyme (TEM) by *Escherichia coli*, after only 1 year. This first generation of β-lactamases produced by *E. coli* (TEM-1, TEM-2) or *Klebsiella pneumoniae* (SHV-1) were countered by administering β-lactamase inhibitors alongside antibiotics (e.g. amoxicillin/clavulanic acid) and by using cephalosporins, which are less easily hydrolysed by β-lactamases. Further selective pressure led to the modification of these first β-lactamases, resulting in extended spectrum β-lactamases (ESBLs) resistant to β-lactamase inhibitors and cephalosporins. Antibiotic-driven selection following the introduction of the carbapenems selected for bacteria capable of producing *K. pneumoniae* Carbapenemase (KPC) and metallo-β-lactamases (MBL).[9]

The three main classes of antibiotics used to target Gram-negative bacteria, (third-generation cephalosporins, fluoroquinolones, and carbapenems) all select for highly resistant strains of bacteria. ABR is a major problem in the hospital environment where these pathogens are common. Some of the most resistant strains, such as multidrug-resistant (MDR) *Acinetobacter*, are selected by all three classes, leaving few options for physicians. A 2009 review of the drug development pipeline found that no new drugs with a pure Gram-negative spectrum had reached clinical Phase II and no drugs targeting carbapenemase-producing organisms were in development.[10]

Table 1: Gram-negative resistance mechanisms and their antibiotic consequences.[7]

Mechanism	Antibiotics affected
Loss of porins	Carbapenems (e.g. imipenem)
β-lactamases	β-lactams (including carbapenems for some β-lactamases)
Increased expression of efflux pumps	β-lactams (e.g. meropenem), fluoroquinolones, aminoglycosides, tetracyclines (e.g. tigecycline), chloramphenicol
Antibiotic modification enzymes	Aminoglycosides, ciprofloxacin
Target-site modification enzymes	Fluoroquinolones
Ribosomal mutations	Tetracyclines, aminoglycosides
Metabolic bypass (use of alternate, uninhibited enzymes)	Trimethoprim, sulphonamides
Lipopolysaccharide mutations	Polymyxins

The Globalisation of ABR

It may be that the true story of globalisation in the late 20th and early 21st century is not one of multinational companies, but rather of MDR pathogens. Just as resistance passes between bacteria through plasmid transfer, so too are new strains transported between countries and continents, carried by unwitting travellers. Quite apart from the introduction via international travel, the global use of antibiotics also selects locally for resistant strains. The Enterobacteriaceae, a family of Gram-negative bacteria important in UTIs, are represented by the final 'E' of the American Society of Infectious Disease's ESCAPE acronym (*Enterococcus faecium, Staphylococcus aureus, Clostridium difficile, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species), formed by the pool of antibiotic-resistant pathogens responsible for the majority of nosocomial infections.[11,12] Data from TEST (Tigecycline Evaluation and Surveillance Trial),[13] a global multicentre surveillance study, shows the presence of ESCAPE bacteria on all continents.

Resistance in Latin America

Latin American data on common uropathogens show that over one-third (36.2%) of *K. pneumoniae* samples express ESBL, and close to 15% of the bacteria are resistant even to carbapenems, leaving only the polymyxins - a class of antibiotic previously contraindicated due to liver toxicity - as the only viable treatment option.[13] Data from 2005-2007 showed more than one-fifth of *E. coli* in Latin America were ESBL producers.[14] In a 2006 Brazilian study, 57.1% of these ESBL-positive bacteria were also resistant to second-generation fluoroquinolones (ciprofloxacin).[15] Data suggest that the trend for ESBL resistance is increasing year by year in *E. coli* and is reflected in other UTI-causing pathogens such as the *Klebsiella* spp.[16] Data covering Latin America as a whole found 24.6% of *E. coli* were ESBL producers and of these, 88.3% were resistant to fluoroquinolones.[13] Given the level of resistance in Latin America, empirical treatment of UTI is challenging and options for oral therapies (fluoroquinolones only) are extremely limited.

Carbapenem-Resistant Bacteria

Due to the prevalence of ESBLs, physicians are pushed towards the use of carbapenems, selecting once again for resistant strains and leading to cross transmission and the spread of resistance. In South America, almost all *Acinetobacter* isolates found in hospital are resistant to carbapenems. There are several emerging forms of carbapenemase: KPC in *Klebsiella* spp and other enterics; MBLs (IMP and VIM) in *P. aeruginosa*; MBLs (VIM and NDM) in enterics; OXA-23/24/58 in *Acinetobacter* sp; and OXA-48 in *K. pneumoniae* and *E. coli*. A study on KPC bacteraemia reported attributed mortality between 13.3% (with combination therapy) and 57.8% (with monotherapy).[17] Other studies have reported a mortality rate of around one in three.[17–19] With crude mortality rates likely to be even higher than the levels reported in these studies, the threat presented by carbapenemase-resistant organisms is clear. NDM-1-producing Enterobacteriaceae, which first emerged in India, have quickly spread to all continents.[20] A 2010 study found only 3% of 37 strains of *E. coli*, tested in the UK and at two sites in India, were susceptible to meropenem.[21] Perhaps of most concern is OXA-48 expression in *K. pneumoniae* which confers resistance to colistin, a polymyxin antibiotic, indicating that this strain is resistant to all available antibiotics, leaving no choice but to use a cocktail of different antibiotics with a mortality of 60–70%.

PREVALENCE OF ABR IN UROLOGICAL BACTERIAL INFECTIONS

When examining resistance in uropathogens, the patient cohort can be broadly separated into community/outpatient and healthcare associated/hospital acquired UTI (HAUTI). It is, however, crucial to note the crosstalk between these two patient cohorts, with 70–80% of MDR UTI entering the healthcare setting from the community.

ABR in Community-Acquired UTIs

Because UTI is treated empirically in the majority of cases, the importance of understanding regional variations in resistance levels and infection prevalence cannot be overstated. Three important studies on community acquired UTI/uncomplicated cystitis (UC) provide data on this subject: the ECO.SENS study, covering Europe and Canada; the NAUTICA study, USA and Canada; and the ARESC study, Europe and Brazil. As would be expected, data from all three studies show that *E. coli* is responsible for the majority of cases of UC (77%, 58%, and 76% in the ECO.SENS, NAUTICA and ARESC studies, respectively).[22–26] In the

ARESC study, no other organism was implicated significantly in >4% of infections.[26]

Table 2 shows data from the ARESC study on the prevalence of resistance in *E. coli* to commonly prescribed antibiotics in ten countries. The common consensus is that any antibiotic with >20% resistance cannot be recommended as an empirical treatment, with a further consensus - although not truly evidence-based - that antibiotics with >10% resistance should not be used for empiric treatment, commonly used for treating more serious infections such as pyelonephritis. Looking at Brazil as our sole source of Latin American data from this setting, we see that only fosfomycin, mecillinam, and nitrofurantoin could be used empirically for both UC and pyelonephritis despite fosfomycin and nitrofurantoin being unsuitable for the latter. Trimethoprim/sulfamethoxazole (TMP-SMX), historically the 'gold standard' treatment for UC, has a far higher incidence of resistance than the empirical threshold in Brazil as well as the majority of other countries investigated.[26] It is for this reason that TMP-SMX is no longer included in international guidelines for first-line empiric treatment of UC.[27]

In terms of the total spectrum of AMR, the three studies are generally comparable, with key drugs for the treatment of UC such as ampicillin and co-trimoxazole having resistance rates usually above the 20% threshold for empiric treatment.[22,24,27] Therefore, these important drugs are no longer recommended for first-line treatment of UC. Reported resistance levels, which are <20% in all studies, would suggest that the fluoroquinolones still represent viable first-line therapies; however, high rates of collateral damage have precluded even these relatively effective therapies from international guidelines.[27] As mentioned, nitrofurantoin, mecillinam, and fosfomycin still have acceptable resistance levels, despite having been used extensively since the 1970s; this may be due to the fact that they have been used exclusively in UC,[22,24,26] but nitrofurantoin's mode of action and the limited geographic use of mecillinam may also play a role.

ABR in HAUTIs

Sources of data on the nosocomial patient cohort are scarce, with only one study, the internet-based Global Prevalence Study of Infections in Urology (GPIU), focusing on HAUTI. The GPIU is, however, a rich data source. The study has an extensive geographical reach, with 56 countries having provided data between 2003 and 2013. Although there are important gaps, such as in the USA, reporting has been particularly strong in Europe and Asia, as well as in South America. Reporting began in 2003 with the study expanding to include side studies focused on antibiotic prophylaxis, transurethral resection of the prostate, prostate biopsy, and surgical site infections. Importantly, a control group has also been present since 2008 to allow for the assessment of risk factors.[28,29]

Table 2: Susceptibility patterns of *Escherichia coli* (%) in ten countries.[26]

Antibiotic	E (515)	F (409)	D (243)	RUS (301)	I (239)	Br (374)	PL (90)	A (62)	NL (29)	H (52)
1. Fosfomycin	97.2	99.0	97.9	99.3	97.9	97.0	98.8	100	100	100
2. Mecillinam	94.1	97.0	97.5	97.3	94.1	94.6	97.7	100	96.5	96.1
3. Nitrofurantoin	94.1	97.3	92.5	94.7	97.4	94.3	92.2	100	100	98.0
4. Ciprofloxacin	88.1	98.2	95.4	87.4	87.0	89.2	92.2	98.3	96.5	92.3
5. Nalidixic acid	73.5	93.6	90.5	82.7	73.6	75.4	84.4	91.9	93.1	67.3
6. Amoxi/clav	77.3	90.9	88.8	83.0	71.9	79.8	85.5	93.5	82.8	51.9
7. Cefuroxime	75.3	89.2	91.3	83.4	78.2	74.5	77.7	77.4	89.6	75.0
8. TMP-SMX	66.2	87.7	74.0	69.4	71.1	54.4	80.0	70.9	79.3	59.6
9. Ampicillin	35.3	60.8	59.2	42.0	43.0	37.7	40.0	43.5	65.5	32.6

■ resistance <10% ■ resistance 10-20% ■ resistance >20%

Amoxi/clav: amoxicillin/clavulanic acid; TMP-SMX: trimethoprim/sulfamethoxazole.

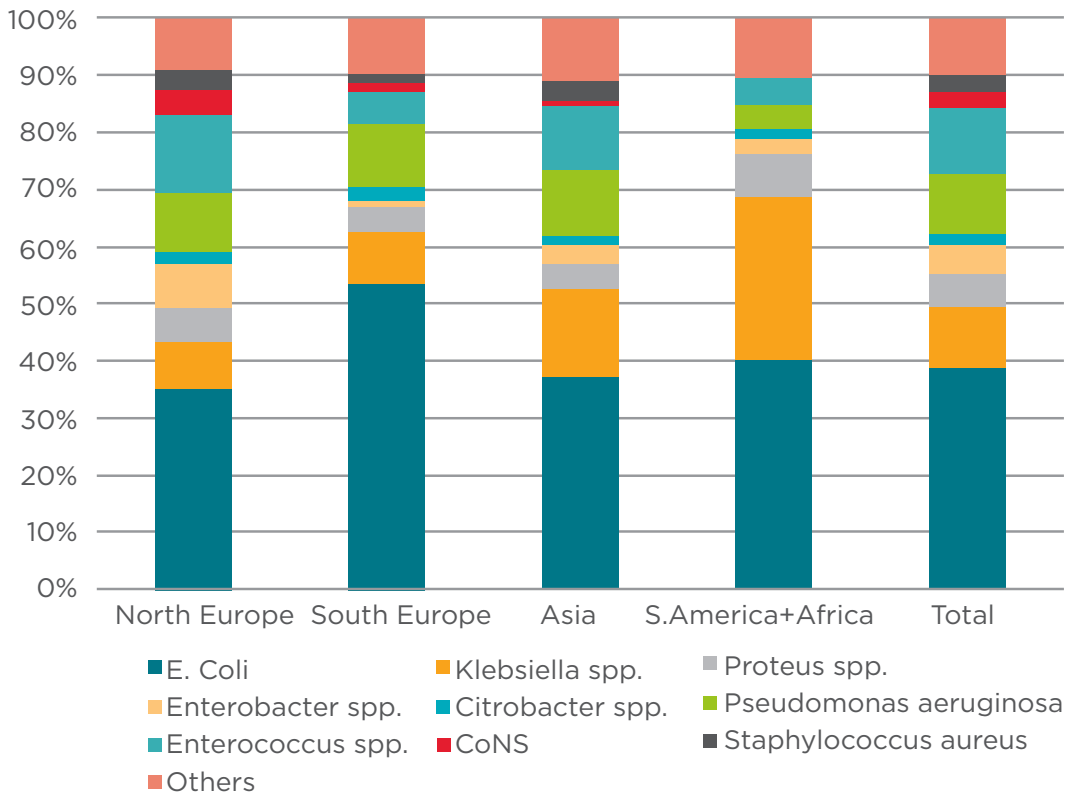

Figure 1: Spectrum of uropathogens in hospitalised urological patients as percentage of the total in different geographic regions.[30]

CoNS: coagulase negative staphylococci.

The next major stage of development will be to extend this study into the community setting, allowing better understanding of resistance rates and the previously mentioned cross-talk between nosocomial and community cohorts. Such an approach will provide other useful information on the management of UTI and recurrences of UC in the community.

Data for the GPIU are collected each year on a single day in November, with participants encompassing all patients on the ward at 8am. Data from all participants are then collected retrospectively up to admission and prospectively until discharge, resulting in a rich longitudinal dataset. Between 2003 and 2010, 19,756 patients were screened, resulting in the enrolment of 1,866 patients with a HAUTI (9.4%). As would be expected in a nosocomial urological setting, males make up the majority of the cohort (70.4%); the mean patient age is 59.9±18.2.[30]

Prevalence of HAUTIs

The GPIU study has revealed some yearly variation in the general rate of HAUTI (approximate mean 11%, range 8–14%), but of more significance is the variation between hospitals, with the rate ranging from 7–21%.[30] University hospitals had the highest rate of HAUTI, which was close to 50%, followed by teaching and district hospitals, respectively. The high rate in university hospitals is likely explained by the increased severity of illness treated in this setting. In contrast to the data from the community, a number of other pathogens alongside *E. coli* (35%) have an important role in HAUTI. Prevalence of *Pseudomonas* HAUTI was 13%, likely driven by the high incidence of catheter associated infection with this species. The high rate of *Klebsiella* infections (10%) is of particular importance given the previously detailed resistance potential of this organism.[16] The Gram-positive *Enterococci* also made up a significant proportion of infections (9%).

Viewing the data geographically further illustrates the importance of region-specific information. HAUTI varied both in terms of the severity of infection and the distribution of pathogens found (Figure 1). Urosepsis was rare in Russia and Hungary, with higher rates in Germany and Turkey. This variation is likely due, at least in part, to the different

healthcare structures present across the globe. *E. coli* was the dominant pathogen in HAUTI in most countries (Germany, Hungary, Turkey, Italy, Greece, South Korea); however in Russia, *Klebsiella* was more prevalent.[30] Global resistance rates, i.e. percentage resistance of the total uropathogenic bacterial strains isolated from a specific site, reveal an extremely worrying - if not totally unexpected – picture, with resistance for all commonly used antibiotics, except carbapenems (at 30–50%). Resistance rates for *E. coli* are high for all commonly used antibiotics, with only the carbapenems at a low enough rate to make them useful as an empiric treatment for severe infection. Of note, there are higher than average levels of resistance found in South America to TMP-SMX (South America, 80%; Global, 50%) and piperacillin/tazobactam (South America, 70%; Global, 22%).[30]

Rates of resistance by hospital setting reflected the picture of prevalence, with higher rates seen in university hospitals and lower in teaching and district hospitals, respectively; again, likely linked to the severity of treated cases. Rates of antibiotic use suggest a delay in treatment patterns behind the evidence. Fluoroquinolones were used to treat 27% of HAUTI despite high resistant rates - 44% and 42% in university and teaching hospitals, respectively - as well as the issue of collateral damage. Carbapenems are already being prescribed in 9% of cases, likely for severe infections. However, this rate is worryingly high given this class of antibiotic represents the final empirical option left for serious HAUTI. Since the rate of urosepsis has risen from 10% in 2003 to 25% in 2011, the need to rely on carbapenems is only likely to increase. [30]

The spectrum of bacteria responsible for the 350 cases of urosepsis is similar to that seen in HAUTI overall, with *E. coli* causing the largest proportion of resistant infections (approximately 30%), followed by *Pseudomonas*, *Klebsiella*, *Enterobacter* spp., and *Proteus* spp. Resistance levels to ceftazidime, piperacillin/tazobactam, and ciprofloxacin were ≥20% for all five of the most common infectious agents responsible for urosepsis (except piperacillin/tazobactam resistance in Proteus spp. at >15%). MDR (non-susceptibility to at least one agent in ≥3 antimicrobial categories) and extensive drug resistance (XDR) (non-susceptibility to ≥1 agent in all but ≤2 antimicrobial categories).[31] Rates were extremely high in this data set. MDR in the *Enterobacteriaceae* as a whole had a prevalence of 51% and XDR of 32%.[30] Knowledge regarding risk factors for MDR and XDR will be important for the next generation of guidelines. Infection with a UTI in the previous 12 months, hospitalisation within the previous 6 months, antibiotic treatment within the previous 3 months, and a greater burden of illness, indicated by higher Charlson Comorbidity Score, were all significant predictors of MDR infection. Only nephrostomy was a positive predictor of XDR.[30]

The above data make clear the challenge faced by urologists who, until now, have been reliant on empirical antibiotic therapy to treat the majority of their patients. It is important for treatment guidelines to adapt and to keep pace with the changing landscape of infectious diseases; clearly antibiotic stewardship - the multifactorial approach aimed at optimising antibiotic treatment and cure - reducing collateral damage and therefore sparing antibiotics, must be at the core of these developments.

GUIDELINES FOR THE MANAGEMENT OF UTI: AN INTERNATIONAL AND LOCAL NEED

The relation between physicians' current practice and guidelines can be complex. They may be seen as intrusive documents which affect long established practices. However, the time constraints placed on the modern clinician, along with ever-changing literature, make the guideline document an essential resource in maintaining best clinical practice. Evidence-based treatment is recognised as the keystone of effective care in modern medicine, and guidelines offer the most efficient way to disseminate up-to-date knowledge to front-line clinicians. However, there are many challenges in the creation and implementation of guidelines at a local and international level, not the least of which is keeping up with the current data.

Challenges to International Guidelines: Definitions and Targeted Therapies for UTIs

There is a tendency within the clinical community to view common urological conditions such as UC as benign conditions that are easily recognised and treated. The need for tailored diagnoses and therapies for specific patient groups with UC is now being recognised.[27,32] Current German guidelines recognise six categories of otherwise healthy

patients with UC: non-pregnant pre-menopausal women (standard group); pregnant women; post-menopausal women; young men; and patients with diabetes mellitus and stable glycaemic metabolism.[32] The international European Association of Urology (EAU) guidelines are close behind with five recognised UC categories.[27] Similarly, treating a large heterogeneous population of patients with more complex UTIs with a single approach will not result in properly targeted and appropriate care. Rapid classification of the risk is essential in order to facilitate the choice of an appropriate treatment regimen. Scoring using the ORENUC host risk factor assessment can quickly allow physicians to assess the potential risk of severe infection in patients with UC and tailor the level of aggression needed in treatment: O – nO known risk factor; R – risk for Recurrent UTI but without risk of more severe outcome; E – Extraurogenital risk factors; N – relevant Nephropathic diseases; U – Urological resolvable (transient) risk factors; C – permanent external urinary Catheter and unresolved urological risk factors.[33]

Host Factors and Symptom Control

In the case of UC, where progression to a serious UTI is unlikely, the first aim of the therapy should be addressing host symptoms rather than eradication of the infectious agent. Recently, a self-reported symptom questionnaire has been created with the aim of improving the assessment of UC symptoms. The purpose of the questionnaire is not only to assess symptoms and their resolution through treatment but also to act as a guide to empirical treatment by aiding differential diagnosis. Questions address symptom assessment/differential diagnosis (i.e. to detect a vaginal infection that is causing the dysuria); quality of life; and a final section of questions to address other conditions which may affect treatment choice.[34] Recognition of the primacy of symptom control in UC is likely to be key in future guidelines.

Treatment Guidelines

UC

According to current EAU guidelines, antibiotic therapy is still recommended for the treatment of UC in otherwise healthy women. The aim of antibiotic therapy is the rapid reduction of clinical symptoms and reduction of morbidity. Evidence shows that the use of short-term therapy is as effective as longer-term therapy. Fosfomycin trometamol (1 day), pivmecillinam (3–5–7 days), and nitrofurantoin (5–7 days) are recommended first-line therapies due to their exclusive use in uncomplicated UTI and consequent reduction in collateral damage leading to resistance. Previously recommended first-line therapies, TMP-SMX (3 days), trimethoprim (5–7 day), and fluoroquinolones (3 days) are no longer recommended empiric first-line therapies due to resistance levels and collateral damage.[27]

Data suggest that short-term therapy is equally effective in post-menopausal women; no difference was found in outcomes between patients with UC treated with 3 or 7-day courses of ciprofloxacin.[35]

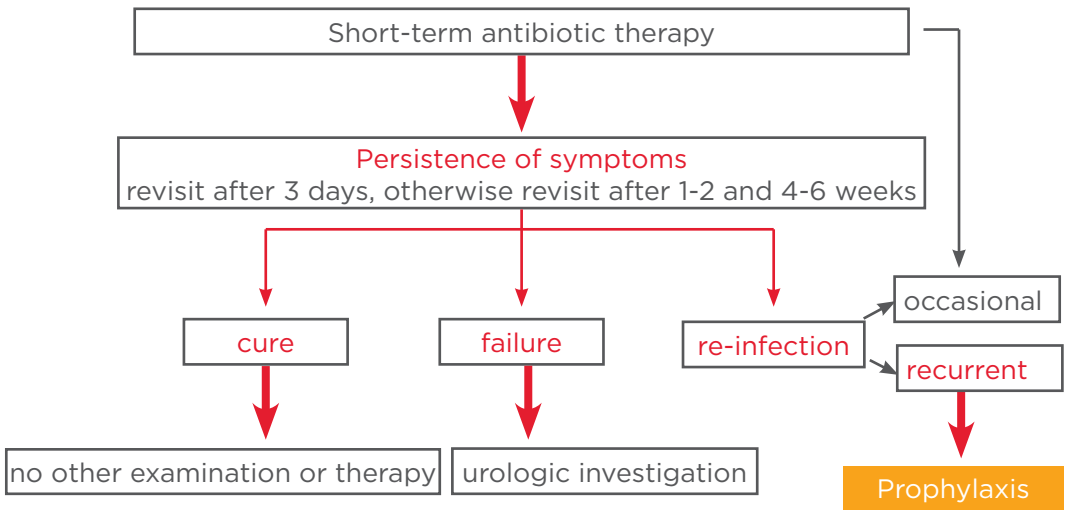

Figure 2: Treatment algorithm of recurrent urinary tract infection.[27]

Care must be taken when considering antibiotic use in pregnancy. TMP-SMX is contraindicated during the first trimester of pregnancy due to its antifolate effects (trimethoprim) and after 32 weeks due to the risk of hyperbilirubinaemia caused by the displacement of bilirubin from albumin (sulfamethoxazole). Nitrofurantoin should be used with caution in the final trimester (FDA, recommendations).[36] In a piloted study of ibuprofen treatment versus ciprofloxacin, ibuprofen was confirmed as non-inferior for the treatment of uncomplicated symptomatic UTI. Day 7 symptom resolution was 75% with ibuprofen and 60.6% with ciprofloxacin (p=0.306).[37] More data are needed and a number of trials are ongoing (ClinicalTrials.gov). It may be that the use of anti-inflammatories for UC will be included in guidelines in the years to come.

Asymptomatic bacteriuria (ASB)

ASB is a distinct condition from cystitis and should not be treated in healthy non-pregnant women. Treatment in healthy young women has been found to increase the chances of recurrence of the following 12 months.[38] Exceptions include pregnancy, where antibiotic treatment is warranted due to the increased risk of progression to serious UTI. Treatment is also indicated in patients who are to undergo urological surgery, due to the risk of traumatic intervention resulting in access of uropathogens to the circulation.[27] However, in patients with complicated conditions, including spinal-cord injury patients, diabetes mellitus, and catheterisation, no benefit in treating ASB has been found.[39,40]

rUTI

In the case of rUTI (defined in the EAU guidelines as at least two documented episodes in 6 months or three in 1 year), EAU guidelines recommend prophylaxis (Figure 2), behavioural modification, followed by alternative non antimicrobial prophylaxis, and finally antibiotic prevention as a last resort when all the other alternative measures have been unsuccessful.[27] For many women, behavioural modification will be unsustainable or ineffective. Besides reducing the burden of disease, the antibiotic sparing effect of non-antimicrobial prophylaxis reduces the likelihood of resistance developing, avoids antibiotic side-effects, protects host microbiota, and reduces the risk of further infections and breaking the antibiotic vicious cycle.

The majority of non-antimicrobial prophylactics assessed in current EAU guidelines have a poor level of evidence and therefore a recommendation Grade C: topical oestrogen (post-menopausal women); oral and intravaginal lactobacillus (with the exception of *Lactobacillus crispatus* [Grade B]); cranberries (different formulations); and injectable immune-prophylaxis. The exception is the oral immunostimulant OM-89 which has a recommendation of Grade B with evidence from both randomised controlled trials and meta-analyses (level of evidence 1a). This immunoactive prophylaxis is also recommended in other current guidelines such as in Russia, Mexico, and Brazil.[27,41]

Guidelines in Latin America

Lack of regular systematic data collection is a challenge for local guidelines due to the lack of knowledge of local levels of ABR, required to advise appropriate empirical treatment. This issue is evident in Latin America where guidelines lack a solid foundation in evidence-based medicine due to sparse data collection within the region. Currently, only three countries in the region have published clinical guidelines for UTI: Brazil, Colombia, and Mexico.

UTIs in Mexico: epidemiology and guidelines

The Mexican Institute of Social Security reported UTI as among the ten leading causes of consultation in family medicine between 2003 and 2008. In the 25–44 year age group, incidence was approximately 6% in 2008, with the high rate thought to be linked to sexual practices or perhaps the use of vaginal soaps affecting commensal flora. The above data suggest rUTI is a significant public health problem within Mexico.[42–44] Mexican guidelines recommend that women with signs and symptoms of uncomplicated lower UTI, without likely bacteriuria from another source, should be treated with antibiotics. Short-term treatment is a key recommendation. The guidelines do not recommend the use of ascorbic acid or other urinary acidifying agents as an adjuvant to the treatment of uncomplicated lower UTI due to poor evidence of efficacy. Monitoring is not required in patients with good therapeutic response. In patients with significant dysuria, supplementary pain relief treatment with phenazopyridine for the first 48 hours (100 mg every 8 hours) is recommended.[45]

In Mexico there are high rates of resistance to TMP-SMX in *E. coli* and a single dose of fosfomycin is recommended as an alternative. As in the international guidelines, fluoroquinolones are no longer recommended as first-line treatment for uncomplicated UTI due to high rates of collateral damage. Further, fluoroquinolones are not recommended in general for patients <21 years of age to avoid adverse effects on cartilage during growth. Tests to rule out structural abnormalities are not recommended in cases of recurrence but care should be taken to identify and reduce patient risk factors. Urine cultures are recommended in some cases to distinguish between recurrence and re-infections. In cases of re-infection, prophylaxis should be considered alongside patient-initiated treatment. Imaging is only recommended in patients who: 1) lack a good therapeutic response; 2) have risk factors for structural abnormalities of the urinary tract; or 3) other evidence suggesting underlying conditions such as urolithiasis or the presence of haematuria.

More recently, a literature review encompassing a large number of studies conducted on UTI in Mexican women from 2005–2010 was carried out by the Mexican Association of Specialists in Obstetrics and Gynaecology. The gathered evidence was assessed in order to formulate recommendations for the treatment and prevention of rUTI. For the treatment of acute infections, nitrofurantoin and fosfomycin are recommended. But the choice of an appropriate antibiotic should be made according to local or regional resistance patterns. The guidelines encourage the use of a urinary culture to determine bacterial sensitivity in patients with recurrence or re-infection before initiation of treatment. The use of prophylaxis is also recommended in this patient group. OM-89 is the sole non-antimicrobial prophylactic measure recommended to reduce the incidence of rUTI (Grade B recommendation).[46]

Recent publications and abstracts evaluating the bacterial resistance in Mexico City in 2006 and in the City of Monterrey between 2002 and 2005, show that resistance to fluoroquinolones and TMP-SMX is already climbing beyond 46%. This recent evidence discourages their use in line with the worldwide data mentioned previously, but individual or case-by-case evaluation is recommended.[47-49] A recent review of cases from 2007-2012 in the Monterrey city area showed a persistent 47% resistance to fluoroquinolones and a 60% resistance to TMP-SMX, further strengthening their discontinuation for regular patient use.[50]

Brazilian guidelines

Brazilian guidelines recommend low-dose antibiotics for rUTI prophylaxis: nitrofurantoin (50 100 mg); TMP-SMX (400 mg); norfloxacin (200–400 mg); ciprofloxacin (250 mg); or pipemidic acid (400 mg). However, the guidelines also recognise the issue of resistance and adverse effects on normal bacterial flora. *In vitro* evidence of cranberry Type A proanthocyanidins shows reduction of bacterial adhesion (80%) from studies conducted in the 1980s. However, long-term tolerability and adherence to treatment is suggested to be a bar to the feasibility of cranberry prophylaxis. The Brazilian guidelines also recommend the use of the immunostimulant OM-89 citing pre-clinical evidence of reductions in oedema, leukocyte infiltration, and haemorrhaging rates in the uroepithelium in a lipopolysaccharide-induced cystitis animal model. The recommended dose is one capsule a day for 3 months. Studies also showed a decrease in the number of recurrences, dysuria, bacteriuria, and pyuria using this dose. OM-89 is available in capsules in Brazil, containing 6.0 mg of lyophilised bacterial lysate.

Colombian guidelines

In Colombia, guidelines focus on UTI associated with catheterisation and control of nosocomial infection. The guideline recommends that unless there are clinical indications, routine use of systemic antibiotics is not indicated in patients requiring a catheter for either a short or long period of time. No prophylaxis management of antimicrobials are mentioned in any section.

CONCLUSION

Antibacterial resistance rates are continuing to increase across the globe, and antibiotic drug development is not keeping pace with the emergence of MDR and XDR strains. Rates of resistance in uropathogenic organisms are worryingly high and empirical treatment options for serious infections are now extremely limited. Recognition of this problem is evident in international guidelines; however, local guidelines and, crucially, front-line prescribing practices do not appear to be changing with sufficient urgency.

Local knowledge of resistance rates is key and the GPIU study points to a possible way forward to allow physicians and epidemiologists to access up-to-date data on resistance rates in the hospital setting and – probably in the near future - on community setting. The importance of prophylaxis of rUTI with alternatives to antibiotics has been recognised and should be included in the guidelines. While the importance of guidelines has been underlined above, they should be recognised as a guide only, and not be allowed to obscure the physician's medical judgement and the individual requiring treatment.

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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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Disclosure: The authors are global consultants of OM/Vifor Pharma Company, Meyrin, Switzerland.
Acknowledgements: Assistance was provided by Ewen Legg, ApotheCom ScopeMedical.
Support: The publication of this article was funded by OM/Vifor Pharma. The views and opinions expressed are those of the authors and not necessarily those of OM/Vifor Pharma.
Citation: EMJ Urol. 2014;1(Suppl 2):14-21.

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.

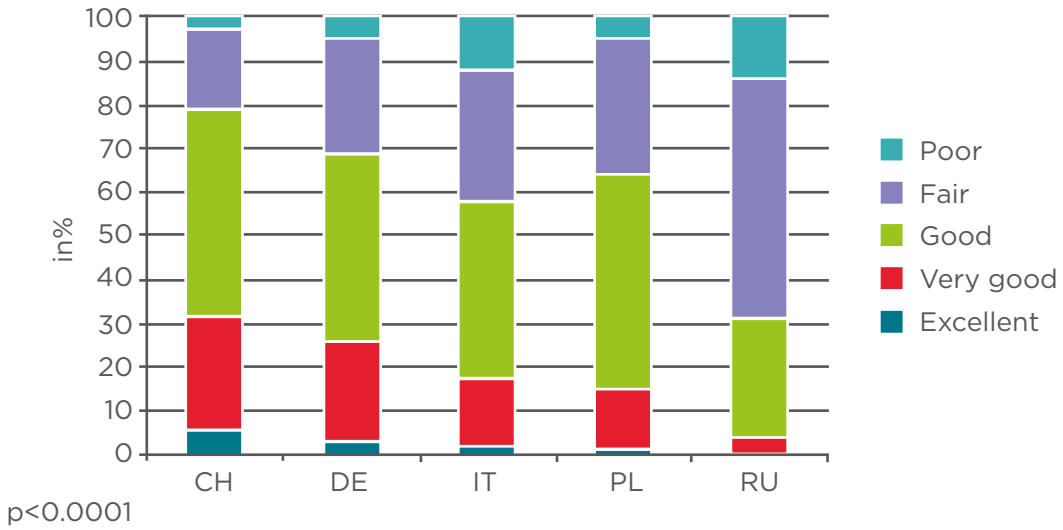

Figure 1: Respondents' general feelings about health.
CH: Switzerland; DE: Germany; IT: Italy; PL: Poland; RU: Russia.

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]

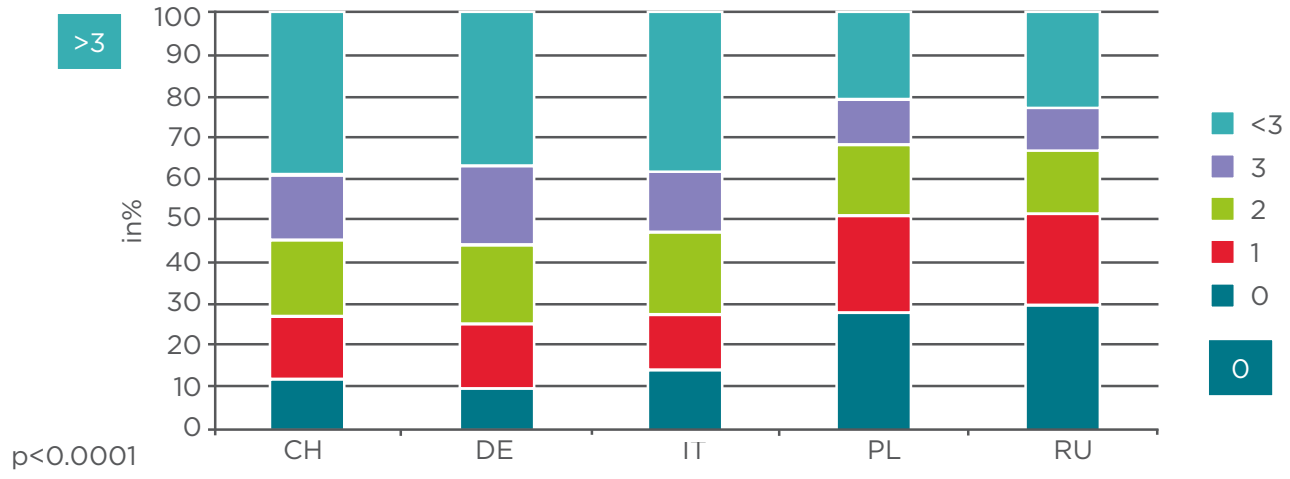

Figure 2: Number of antibiotic prescriptions received in the last year for urinary tract infection.
CH: Switzerland; DE: Germany; IT: Italy; PL: Poland; RU: Russia.

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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RECURRENT URINARY TRACT INFECTIONS: CAN IMMUNOACTIVE PROPHYLAXIS IMPROVE DISEASE MANAGEMENT IN HEALTHY WOMEN?

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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Disclosure: The authors are global consultants of OM/Vifor Pharma Company, Meyrin, Switzerland.
Acknowledgements: Writing assistance was provided by Ewen Legg, ApotheCom ScopeMedical.
Support: The publication of this article was funded by OM/Vifor Pharma. The views and opinions expressed are those of the authors and not necessarily those of OM/Vifor Pharma.
Citation: EMJ Urol. 2014;1(Suppl 2):22-28.

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.

UTIs are one of the most prevalent bacterial infections and are the most common type of infection in healthy adult women, affecting 50% of them at least once in their lifetime.[1] The level of antibacterial resistance in common uropathogenic organisms is reaching alarming levels[2] and the importance of prophylaxis in the context of increasing resistance cannot be overstated. The current three-tiered approach taken by the European Association of Urology (EAU) for UTI prevention consists of: counselling and behavioural modification, followed by non-antimicrobial prophylaxis, and eventually antimicrobial prophylaxis.[3] For many women, counselling and behavioural modification will not be enough to prevent rUTIs, resulting in a need for effective non-antimicrobial therapies which spare antibiotic use and reduce the risk of engendering further resistance in uropathogens. OM-89, a bacterial-lysate-based therapy, currently has the grade of recommendation B in the EAU guidelines for non-antimicrobial prevention of rUTI in otherwise healthy women.[3] In the following report we will summarise the putative immunostimulatory mechanism of OM-89 and review the evidence for its efficacy in preventing rUTIs in healthy pre and post-menopausal women.

IMMUNOSTIMULATORY MODE OF ACTION OF OM-89

The host defences of the urinary tract can be divided into first and second lines of defence. The first line of defence is further subdivided into mechanical defences (the physical barrier of the uroepithelium and urinary flow) and innate aspecific immunity. Innate immunity is congenital, and characterised by a rapidly mounted inflammatory response. It is mediated via pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), which recognise pathogen-associated molecular patterns (PAMPs) and recruit phagocytic leukocytes

and granulocytes.[4] Perhaps the most well-known PAMP is lipopolysaccharide (LPS), which has long been recognised as a potent inducer of inflammatory response in mammals, which is recognised by the PRR TLR4. The second line of defence is adaptive/specific immunity. Adaptive immunity responds to specific pathogen-derived antigens with a targeted response. It involves multiple cell classes and is characterised by a slow activation, though responses may be rapid in later stages. The stages of adaptive immunity include: uptake of antigens by antigen-presenting dendritic cells (DCs); activation of T cells; B cell formation (conveying humoral immunity); and homing of immune cells.

Challenges for the Immunostimulatory Approach

Direct stimulation of the immune system has been proposed as an alternative to antibiotic repeated treatment cycles and prophylaxis for UTIs. One of the principal challenges to this approach is posed by the variety of infective agents responsible for UTI. Although the vast majority (approximately 80%) of uncomplicated cystitis is caused by uropathogenic *Escherichia coli* (UPEC),[5,6] there are thousands of UPEC clones/strains, each with a unique antigen profile. This makes the selection of a single antigen likely to lead to broad immune response against UPEC infection challenging.[7] Attempts have been made at vaccination using single antigens shared by the majority of UPEC strains, such as the adhesion protein FimH or specific iron-uptake receptors. Inoculation with the virulence factor FimH has shown some success *in vivo*.[8] However, this has yet to translate to a workable human vaccine, perhaps due to FimH expression being subject to phase variation, allowing evasion of the humoral response.[7]

Iron uptake is essential for bacterial infection and vaccines against iron-uptake receptors have shown some promising results in *in vivo* models of sepsis[9] and have elicited immune response in the mouse kidney.[10] However, protection against UTI was not conferred by immunisation against iron-uptake receptors, likely due to a lack of detectable levels of immunoglobulin A (IgA) in the bladder.[10] Data on the role of the adaptive immune system (AIS) in acute lower UTI are sparse; however, results suggest it is less important than in related conditions such as pyelonephritis.[7] This may be a factor in the current lack of success with antigen-specific vaccination, suggesting another approach may be required. The use of extracts from inactivated UPEC strains is one such alternative approach. These extracts contain a multitude of antigens and PAMPs likely to facilitate activation ofboth the innate and AIS.[11] In the case of OM-89, the extract is comprised of the lysate of 18 UPEC strains and has shown efficacy in rUTI prophylaxis. Experimental studies investigating activation of both the innate and AIS by OM-89 have now generated evidence of activation at multiple stages of the immune response.

Activation of the Innate Immune Response by OM-89

In vitro studies investigating the effects of OM-89 exposure on human cell lines expressing specific PPR (TLRs or Nod-like receptors) reveal a concentration-dependent activation of human TLR2 and TLR4.[12] There is extensive evidence for the role of TLR4 in the response against UTIs.[7,13] Both OM-89-induced stimulation of murine spleen cells - a key source of macrophages for the innate immune system[14] - and increased metabolic and phagocytic activity in circulating human leukocytes, isolated from peripheral blood, following incubation with OM-89 have been demonstrated *in vivo*. Furthermore, there was a 30% reduction in spontaneous apoptosis of human granulocytes incubated with OM-89, suggesting a mechanism involving both activation of the innate immune system and perpetuation of its activity.[15]

Activation of the Adaptive Immune Response by OM-89

Antigen-presenting DCs are activated following PAMP recognition by PRRs and are a crucial bridge between the innate and AIS.[11] Circulating DCs capture and process antigens in the periphery before migrating to lymphoid organs and releasing cytokines to initiate adaptive immune responses.[16] Human monocyte-derived DCs exposed to OM-89 *in vitro* show a concentration-dependent increase in expression of the co-stimulatory protein CD83,[17] an important marker of DC maturation.[18] The role of mature DCs in stimulating T helper cell proliferation and interferon gamma production provides a possible mechanism for the activation of adaptive immunity by OM-89.[17,19] OM-89 has been shown to be an activator of polyclonal murine B lymphocytes.[20,21] In mice, both intraperitoneal and oral application of OM-89 stimulate production of antibodies, which bind strains of *E. coli* present in the OM-89 lysate, and immunogenicity has been

localised to the urogenital tract following repeated oral administration.[21,22] Increased levels of total and strain-specific IgG and IgA were detected in the supernatant of cell culture prepared from the urogenital tract of immunised mice, suggesting the creation of a protective barrier at the mucosa level of the urinary tract.[20–22]

In a murine model of *E. coli* infection-induced cystitis, oral pre-treatment with OM-89 led to a concentration-dependent reduction in the number of viable bacteria, as measured by colony forming units.[22] Notably, serum from mice treated with oral OM-89 was active not only against all 18 strains present in the lysate but also against a number of other uropathogenic microorganisms and other unrelated bacteria.[15,22,23] Stimulation of adaptive immunity has also been demonstrated in a human study of 38 paediatric patients with rUTI. Administration of OM-89 alongside antibiotic prophylaxis led to a 65% (p=0.02) increase in secretory IgA in urine at the end of the 6-month study. This increase has not been seen in the control group.[24] Finally, there is histological evidence of the protective effects of oral therapy with OM-89 in a murine model of LPS-induced cystitis. Mice treated for 10 days before induction of cystitis had a significant reduction in their bladder inflammatory index compared with untreated mice.[25]

Summary

Oral treatment with OM-89 activates an innate immune response and stimulates maturation of DCs - the key bridging cells between innate and adaptive immunity. Adaptive uropathogen-specific immunity has been located to the urinary tract, and reduced viability of *E. coli* and reduced LPS-induced inflammation has been demonstrated. Hence, the above data provide a viable theoretical framework for the immune system cascade, leading from oral treatment to activity in the bladder and clinical efficacy of OM-89 against rUTI.

CLINICAL EFFICACY OF OM-89 IN HEALTHY PRE-MENOPAUSAL WOMEN

Evidence for the clinical efficacy of OM-89 prophylaxis against rUTI exists at various levels, up to and including meta-analyses. Six randomised controlled trials (RCTs) of OM-89 versus placebo have been carried out in otherwise healthy adults - mainly women from 18 years of age. The majority of these featured a 3-month dosing period with patients followed up to 6 months from study commencement,[26–29] with one study extending follow-up to 11 months.[30] There was also a single 12-month study investigating the efficacy of using booster doses for longer term prophylaxis.[31] The trials demonstrated a mean reduction in recurrences of 30–50% with good tolerability.[26–31]

Illustrative Data from Single Randomised Trials

Study design, safety, and efficacy were broadly similar in the 6-month randomised studies. In the Schulman et al.[27] trial, 160 patients (84% female, mean age 45.2 years), with a history of ≥2 UTIs in the preceding 12 months, were enrolled. A highly significant, almost 50%, decrease (58 versus 114, OM-89 and placebo, respectively, p<0.0001) in the number of UTIs (defined as 10^5 bacteria/mL urine) was achieved at 6-month follow-up. There was a similarly marked reduction in mean days spent on antibiotic treatment in the group receiving OM-89 prophylaxis (3.0 versus 6.3 days, OM-89 and placebo, respectively, p<0.0001). Improvements in typical signs and symptoms were also reported, with a favourable benefit–risk profile. A chi-square test on all data to determine overall treatment benefit against placebo gave a significant outcome in favour of OM-89.[27]

In the single 12-month study carried out thus far, patients received 3 months initial treatment followed by a 3-month observation period. During months 7–9, daily booster doses were administered for 10 days and patients were followed up for a further 3 months. In total, 453 female patients aged 18–65 years with a history of ≥3 UTIs in the preceding 12 months were enrolled. Over the 12-month study period, the cumulative rate of UTI was 34% lower in the group treated with OM-89 (p<0.003). The number of patients who did not suffer a recurrence was also higher in the OM-89 group (55% versus 42%, OM-89 and placebo, respectively, p=0.0013) and antibiotic consumption was reduced by 13% (p=0.005). As with the above shorter duration trial, OM-89 was well tolerated.[31]

The above evidence from single trials shows OM-89 to be a well-tolerated UTI prophylactic and antibiotic-sparing therapy with efficacy over 6 and 12 months. Data from the above trials have been synthesised in three meta-analyses.[32–34] Meta-analyses represent the highest level of evidence available to clinicians and clinical scientists, allowing amelioration of bias which may be present in single studies and, in some cases,

revealing novel efficacy or safety-related data due to the increased statistical power derived from larger group sizes.

Meta-Analysis of the Efficacy of OM-89 and other Prophylactic Measures

In 2002, Bauer and colleagues[32] carried out a meta-analysis which included data from women enrolled in the five RCTs of 6-month duration mentioned above;[26–29,32] data from 601 women were analysed in total. OM-89 was found to be superior in reducing UTIs across all studies versus placebo (Figure 1). Symptoms of UTI, dysuria, bacteriuria, and leukocyturia, were all found to be significantly improved in patients treated with OM-89. Improvements compared with placebo were found to be both statistically significant and clinically relevant for all outcome measures mentioned above. The Mann–Whitney summary statistic also demonstrated the superiority of OM-89 with a medium-to-large overall effect size (0.684). Compliance and tolerability were deemed good across all trials by study investigators.[32]

In a second meta-analysis by Naber and colleagues,[33] data from the 12-month study - alongside those from four of the 6-month studies - were deemed suitable for inclusion, comprising 1,000 adult patients.[27–29,31,33] Results were similar to the above analysis, with a mean reduction in the number of UTIs across all studies of 36% at the 6-month time point ($p<0.00001$) and 39% at combined study endpoint in patients treated with OM-89 ($p<0.00001$). More OM-89 patients were free of UTI at combined study endpoint (65% versus 45%, OM-89 versus placebo, $p<0.001$) and antibiotic consumption was significantly reduced with a small-to-medium effect size (standardised mean difference, -0.29). As in the Bauer meta-analysis,[32] there were significant improvements in symptoms and laboratory findings. The side-effect profile of OM-89 was comparable with placebo, with slightly more frequent adverse events in the OM-89 group compared with placebo (+0.8%).

A key result from the Naber et al.[33] study came from the plotting of the mean number of episodes of UTI, with OM-89 as a function of the number of episodes with placebo, which revealed that the studies with the largest number of UTIs in the placebo group were those showing the largest benefit from OM-89. This suggests that patient groups that are more likely to have multiple incidents of recurrence are most likely to benefit from OM-89. It is also worth noting that having a UTI within the previous 12 months is a risk factor for emergence of multi-drug resistant (MDR) infection.[2] Thus, OM-89 may reduce infection most in the group at highest risk of MDR infection, and further improve antibiotic stewardship as a result.[33]

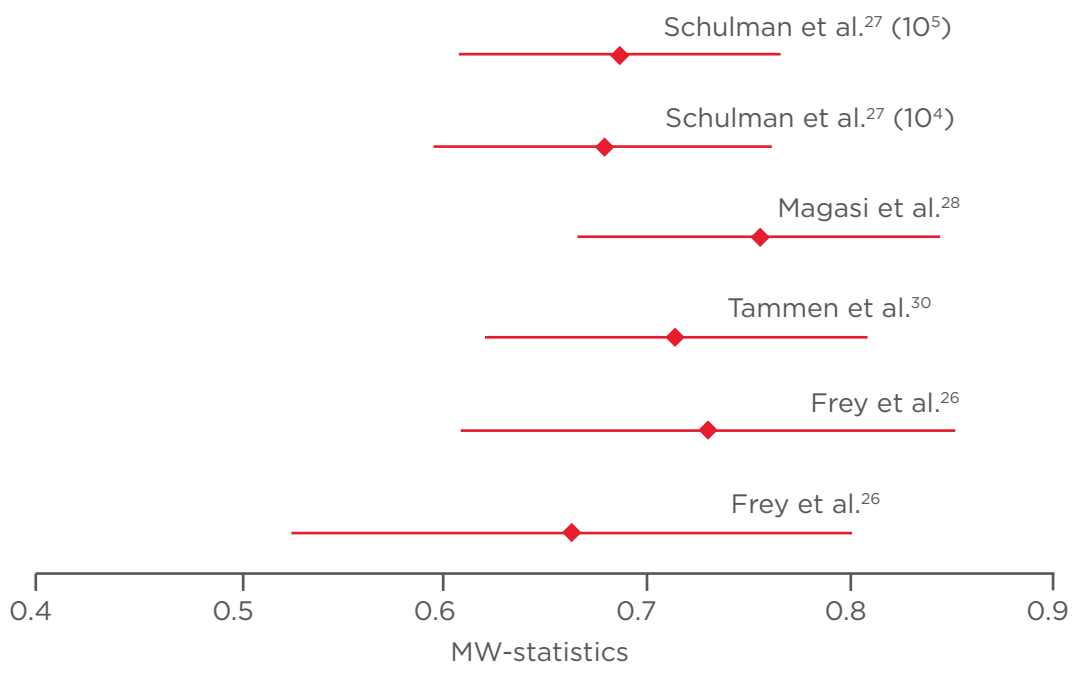

Figure 1: Mann–Whitney (MW) statistical analysis of placebo-controlled trials of OM-89 prophylaxis.
Adapted from Bauer et al.[32]

The final meta-analysis included a number of other prophylactic measures alongside OM-89; 5,413 records were identified and included 17 studies with data for 2,165 patients. Seven prophylactic strategies were identified including: OM-89, vaginal vaccine, vaginal oestrogens, cranberry, and acupuncture. OM-89 reduced UTI recurrence (RR=0.61, 95% CI: 0.48–0.78), with a promising efficacy and a good safety profile. The other results were considered tentative and requiring further corroboration. Vaginal vaccine slightly reduced UTI recurrence (RR=0.81, 95% CI: 0.68–0.96). Vaginal oestrogens showed a trend towards preventing UTI recurrences (RR=0.42, 95% CI: 0.16–1.10) and vaginal irritation in 6–20%. Cranberry decreased UTI recurrence and acupuncture reduced recurrences (RR=0.53, 95% CI: 0.33–0.83 and RR=0.48, 95% CI: 0.29–0.79, respectively).[34]

Summary

Data from six placebo-controlled trials, and three meta-analyses, indicate that OM-89 is a non-antibiotic prophylactic strategy showing robust efficacy against rUTI in healthy adults, mainly women. OM-89 prophylaxis shows promising results as an antibiotic sparing strategy, and appears to have greatest efficacy in the group of women with highest clinical need.

CLINICAL EFFICACY IN HEALTHY POST-MENOPAUSAL WOMEN

There is an increase in the risk of UTI and bacteriuria with increasing age. Post-menopausal women can be subdivided into healthy 50–70-year-olds who are neither institutionalised nor catheterised (lower risk) and elderly institutionalised women who are, in many cases, catheterised.[35] Physiological and clinical features of the latter group, particularly catheterisation, require consideration and affect treatment options and outcomes. In the following section we will concentrate on the former group of healthy post-menopausal women.

Risk Factors for UTIs in Post-Menopausal Women

The predisposing factors for rUTI vary with age. In pre-menopausal women, factors relating to sexual intercourse such as increased frequency, use of spermicide, and having a new sexual partner are predominant. While in post-menopausal women, the predominant factors are age related, including oestrogen deficiency, urinary incontinence, and pelvic organ prolapse with voiding dysfunction. In post-menopausal women, oestrogen deficiency can lead to alterations of the urogenital tract mucosa and promote more frequent UTI. There is a putative link between decreased oestrogen, reduced vaginal lactobacilli, increased vaginal pH, and increased colonisation with *Enterobacteriaceae* coming from the peri-anal region. However, it is important to note that this relationship is controversial due to the presence of conflicting data.[35] Older women with rUTI are likely to have been exposed to antibiotics for longer periods which may contribute to increased vulnerability to infections.[36] Antibiotics, by eradicating the periurethral and vaginal flora, may inadvertently enable colonisation, and hence infection, by new uropathogens. Theoretically, older patients could also be more prone to infections due to the effects of ageing on the immune system allowing uropathogens to more easily colonise the uroepithelium.

Prophylaxis Against rUTIs in Post-Menopausal Women

The theoretical higher risk of rUTI in post-menopausal women makes prophylaxis a key strategy in this group. We have already mentioned the three-tiered approach to prevention, recommended by the EAU. This approach, 1) employing counselling and behavioural modification; 2) non-antimicrobial prophylaxis; and 3) antimicrobial prevention, is aimed at sparing antibiotic use and preventing the development of resistance.[3] Risk factors in post-menopausal women tend to be related to age rather than to modifiable behaviours (e.g. spermicide use in younger women). As a result, the first tier of EAU recommendations may be less effective in post-menopausal women, leading to a greater need for non-antimicrobial prophylaxis, including prevention with immunoactive therapy such as OM-89.

Some of the trials summarised above[27,31] enrolled post-menopausal participants; however, only a single study investigating OM-89 prophylaxis specifically in post-menopausal women with rUTI has been carried out.[37] This was a small, observational, open-label, active control study with a duration of 9 months. The UTI rate was determined retrospectively for the 6 months before treatment initiation. Patients received a single capsule of OM-89 daily for 3 months, followed by a 3-month observation then 10 days of booster

dosing for each of the last 3 months. Subjects were post-menopausal women (n=55; mean age, 66.3 years) with rUTI, including some who were not receiving hormone therapy. Efficacy outcomes included the number of recurrences before and after the immunotherapy and the severity of dysuria.[37] The incidence of recurrences fell from 3.4±1.14 in the 6 months preceding oral immunotherapy to 1.8±1.59 during the 9-month monitoring phase, representing a 64.7% reduction in the recurrence rate in the 55 women receiving oral therapy. In a subgroup of women with higher risk of infection (n=41) (defined as having had >2 UTIs in the previous 6 months), mean rate of recurrences fell from 3.9±0.81 to 2.0±1.66: close to a 70% reduction.[37] This result agrees with the results from Naber et al.,[33] suggesting that patients with the highest rate of UTI may benefit the most from OM-89 prophylaxis.[33]

Summary

The higher risk of UTI in post-menopausal women and the nature of risk factors, which are less amenable to amelioration with behavioural measures, make non-antimicrobial prophylaxis a key tool in preventing infection and sparing antibiotic use in this population. Results from the single study on OM-89 prophylaxis carried out in this group concur with those carried out in healthy adults, mainly women. Importantly, high-risk patients with a recent history of UTI showed a greater reduction in recurrences, suggesting that patients with the greatest clinical need, and at highest risk of urological infection, may benefit most from OM-89 prophylaxis.

CONCLUSION

The immune-stimulant oral prophylactic OM-89 activates both the innate and AIS, boosting host defences against UTI. OM-89 has shown efficacy in both healthy pre and post-menopausal women affected by rUTI, reducing the number of recurrences and laboratory signs and symptoms of cystitis. The increased effect reported in high-risk individuals combined with OM-89's antibiotic sparing qualities, make this prophylactic measure an important resource for physicians tasked with antibiotic stewardship in the context of increasing antibiotic resistance of uropathogens.

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URINARY TRACT INFECTION IN SPECIFIC POPULATIONS AND CONTROVERSIES IN DISEASE MANAGEMENT

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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Disclosure: The authors are global consultants of OM/Vifor Pharma Company, Meyrin, Switzerland.
Acknowledgements: Assistance was provided by Ewen Legg, ApotheCom ScopeMedical.
Support: The publication of this article was funded by OM/Vifor Pharma. The views and opinions expressed are those of the authors and not necessarily those of OM/Vifor Pharma.
Citation: EMJ Urol. 2014;1(Suppl 2):29-40.

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.

The physiological and anatomical changes associated with pathological and non-pathological conditions, such as pregnancy, can modify both the risk of contracting a UTI and the recommended treatment. Risk factors also evolve across the lifespan of a patient affecting the management of UTIs. Here we discuss specific challenges in disease management across a number of patient subgroups at higher risk of UTI.

UTI IN PREGNANCY

Safe and effective disease treatment and prophylaxis during pregnancy is a complex issue due to the dual, and in some cases conflicting, needs of mother and foetus. A number of anatomical and physiological changes occur during gestation that can influence the frequency and outcome of UTIs. These include rotation and dilation of the uterus, increased kidney volume, and physiological immunosuppression. Women with a history of UTI are known to be at higher risk of infection during pregnancy than those with no history, and the consequences of infection may be significantly more serious than in non-pregnant women.[1]

Asymptomatic Bacteriuria (ASB) during Pregnancy

There is now a clinical consensus that ASB is benign in the general population, and may even confer protection against UTI, and, with the exception of some special conditions, should not be treated.[2] However, a strong body of evidence indicates that ASB during pregnancy is related to adverse perinatal outcomes,[1,3] including increased risk of low birth weight, preterm birth, and even

neonatal death.[3,4] The potential for serious clinical complications related to ASB is not restricted to the foetus. The risk of ASB-associated pyelonephritis during pregnancy is 20–40%, compared with 1–2% in non-pregnant women.[2] Pyelonephritis is one of the most serious infectious diseases during pregnancy, owing to the increased risk of sepsis and respiratory distress.

Screening for ASB is recommended by international guidelines,[2,5] although there is currently disagreement as to whether this screening should take place during the first[2] or second[5] trimester. The applicability of these screening guidelines worldwide is questionable given the large variability in ASB rates, particularly between developed and developing countries. A study in Nigeria showed an infection rate of approximately 45%, compared with 2–10% in the USA.[6,7] Antimicrobial treatment of ASB is recommended, followed by monitoring in order to avoid pyelonephritis (Table 1).[2] A short (3-day) course of antibiotics is recommended for the treatment of ASB and choice of antibiotic should be carefully considered.[2] For example, trimethoprim/sulfamethoxazole is contraindicated both during the first trimester of pregnancy due to antifolate effects, and after 32 weeks due to the risk of hyperbilirubinaemia via displacement of bilirubin from albumin.[8] The ORACLE study, a randomised controlled trial (RCT) of antibiotic therapy for pre-labour rupture of the foetal membranes, followed infants up to the age of 5 years, and found that treatment over 10 days may result in mental retardation and cognitive delays.[9,10] However, these results require confirmation by further studies.

UTI Prophylaxis during Pregnancy

Prophylactic strategies for UTI during pregnancy include: post-coital antibiotic therapy (less antibiotic use in comparison with daily prophylaxis) for patients with a previous history of UTI; cranberry juice (36 mg of proanthocyanidins [PAC]) - a Cochrane review of cranberry prophylaxis for UTI in general notes that obtaining a sufficient dose of PAC can be problematic;[11] continuous monitoring; and in some geographic regions, despite clear evidence of effectiveness, 100 mg ascorbic acid.[12,13] A large Norwegian survey found no increased risk of malformations associated with self-administered cranberry, but did detect a possible association with vaginal bleeding after 17 weeks of pregnancy.[12]

In a trial of nitrofurantoin in pregnant women with a history of pyelonephritis during gestation, treatment was not found to be superior to continuous monitoring. However, as patients with poor clinic attendance tend to have more symptomatic recurrences, the monitoring itself may have had a positive effect on reducing recurrence.[13] Assessment of antibiotic prophylaxis studies found most to be outdated and of poor quality.[13] A large randomised trial underway in the Netherlands, that addresses both prophylaxis via screening and treatment with nitrofurantoin (5 days) for ASB, should partially address the current lack of high-quality contemporary data. The study will follow children long-term, providing important safety data on short-course antibiotic treatment.[14]

Table 1: Treatment regimens for asymptomatic bacteriuria and cystitis during pregnancy.[2]

Antibiotic	Duration of therapy	Comments
Nitrofurantoin	q12 h, 3–5 days	Avoid in G6PD deficiency
Amoxicillin 500 mg	q8 h, 3–5 days	Increasing resistance
Co-amoxicillin/clavulanate	500 mg q12 h, 3–5 days	
Cephalexin 500 mg	q8 h, 3–5 days	Increasing resistance
Fosfomycin 3 g	Single dose	
Trimethoprim	q12 h, 3–5 days	Avoid trimethoprim in first trimester

G6PD: glucose-6-phosphate dehydrogenase.

The oral immunostimulant prophylactic OM-89 has a robust evidence base for efficacy in reducing rUTI in non-pregnant women.[15–17] In a small pilot study of 62 pregnant patients with acute UTI (weeks 16–28), daily prophylactic treatment with OM-89 reduced rUTI incidence from 52.5% in the 6 months observation prior to study entry to 19.4% during the study (p=0.002). OM-89 was well tolerated and all newborns were healthy with normal Apgar scores. OM-89 also had a significant antibiotic sparing effect, reducing the proportion of patients requiring antibiotics from 55.7% before, to 12.9% during the study (p=0.0002).[18] Currently, no studies of OM-89 prophylaxis have been performed during the first trimester of pregnancy. No direct or indirect harmful effects on pregnancy, embryonal/foetal development, parturition, or postnatal development have been detected in animal studies. However, we need more evidence to support the use of the product in this patient population. As a precautionary measure, it is preferable to avoid the use of OM-89 in pregnancy.

Summary

Implementation of guidelines on screening and treatment of ASB in pregnant women are key to protecting this high-risk group against serious UTIs. As yet there is no strong evidence-based prophylactic therapy for ASB or rUTI in pregnancy. The understandable reluctance of pregnant women to take part in clinical trials, particularly when otherwise healthy, makes research in this area challenging. However, ongoing trials such as the Dutch-based Kazemier[14] study above show that recruitment is possible and efforts should be made to investigate further promising prophylactic therapies such as OM-89. Furthermore, reporting pregnancies occurring during OM-89 prophylaxis will provide safety data on women, foetus, parturition, and postnatal development, when incidentally exposed to the drug.

rUTI IN CHILDREN AND ADOLESCENTS

UTIs are common in both children and infants. The prevalence of UTIs in the paediatric population is around 5%, with an annual incidence in patients from 0–14 years old of 1.7/1,000 in boys and 3.1/1,000 in girls. UTIs are more common in males only during the first year of life (3.9% higher incidence). UTIs in children are often difficult to diagnose as, unlike in adults, the signs and symptoms are non-specific. Currently, management is complex and places a great burden on healthcare systems, patients, and their relatives.[19]

Paediatric UTI: Symptoms, Diagnosis, and Pathology

UTIs in children <2 years old are always considered complicated. Signs and symptoms are non-specific but include foul-smelling urine and difficulty obtaining urine for urinalysis due to anatomical abnormalities. Recurrences after the first UTI are likely to be frequent (girls 40%, boys 32%) and there is a high risk of urethral scarring (40–70% in febrile UTI). In children >2 years, high fever without a focus is common alongside impaired general condition and foul-smelling urine. There may also be changes in urination and children may report urgency, a feeling of incomplete emptying (vesical tenesmus), and dysuria. In some cases, diffuse abdominal pain, nausea, and vomiting may also be present.

Sampling and urinalysis are important in diagnosis. The definition of a positive culture will depend on the collection method: $>10^5$ colony-forming unit (CFU) for clean catch, $>10^4$ CFU for catheterisation, and $<10^4$ CFU for suprapubic aspiration. Pathological urinalysis confirming >6–8 leukocytes/high power field, the presence of leukocyte esterase, or the presence of nitrites are also positive signs of UTI. Various imaging techniques are also useful in the diagnosis of UTI and concomitant anatomical abnormalities. Techniques include: kidney and bladder ultrasound (US), voiding cystourethrogram (VCUG), diethylenetriaminepentaacetic acid scan, dimercaptosuccinic acid (DMSA) scan, and urethral valve imaging. Useful guidelines for both treatment and diagnosis have been produced by the American Academy of Pediatrics (AAP) in the USA[20] and the National Institute for Health and Care Excellence in the UK.[21] AAP guidelines for diagnosis recommend observation only following a first febrile UTI with a normal US. In case of an abnormal US or rUTI, VCUG should be performed. DMSA is not recommended despite data suggesting that this diagnostic technique may be more accurate in some conditions.[22]

In infants, 30–40% of UTIs are caused by vesicoureteral reflux, a condition that predisposes to further infections and renal damage, which can lead to hypertension and renal failure.[23] Diagnosis is by VCUG, and both medical and surgical treatment options are available. Dysfunctional elimination syndromes are common alongside reflux and will

delay resolution if not addressed.[24] Other common pathologies leading to UTI in children include urinary obstruction, voiding dysfunction, and constipation. Urinary obstruction is associated with a number of syndromes including: ureteropelvic junction obstruction (a congenital obstruction where the ureter joins the renal pelvis); megaureter, an enlarged ureter (a consequence rather than a cause of primary anatomical obstruction); and ureterocele, a congenital abnormality often associated with a duplicated ureter. It is worth noting that these obstructive syndromes may also be associated with vesicoureteral reflux. Other diseases that may be associated with UTI in children include neurogenic bladder dysfunction (NBD), non-NBD, bladder diverticulum, posterior urethral valves, and immunoglobulin A (IgA) insufficiency.

Paediatric UTI: Treatment and Prophylaxis

Following accurate diagnosis, antibiotic treatment is recommended for UTI in children. Amoxicillin/clavulanic acid, sulphonamides, cephalosporins, and nitrofurantoin are typical treatments for uncomplicated UTI. While for complicated UTI, aminoglycosides and third-generation cephalosporins are the standard approach. Assessment and treatment of underlying conditions contributing to rUTI are instrumental in successful resolution. In the case of prophylaxis, meta-analysis of the available evidence suggests that routine neonatal circumcision does not prevent UTI.[25] Antibiotic prophylaxis is not recommended for UTI in children due to low efficacy, side-effects, and contribution to increased antibiotic resistance in the population.[26–28] There is some conflicting advice on prophylaxis in children with vesicoureteral reflux: the American Urological Association suggests prophylaxis in children <1 year old, while recognising that the evidence base is weak,[29] though a recent Cochrane review does not recommend antibiotic prophylaxis due to the risk of resistance.[30]

Progress is being made towards creating viable vaccines against UTIs.[31] Data suggest that systemic rather than local immune response is more important in children than adults,[32] and a small trial has shown inactivated uropathogens have efficacy in reducing UTI.[33] The oral immunostimulant OM-89 is licenced for the prevention of rUTI in adults and children ≥4 years old. In an open-label, randomised, pilot study of OM-89 versus nitrofurantoin prophylaxis, 40 girls (mean age 6.5 years, range 2–10) with a history of ≥3 UTIs in the previous year were enrolled. All received nitrofurantoin (1 mg/kg) during a 6-month run-in phase before one group was switched to OM-89 for a 6-month treatment phase while the other continued to receive nitrofurantoin. Participants were followed for 6 months after treatment and the number of UTIs, dysuria, and bacteriuria/pyuria were recorded. There was a highly significant reduction in UTI recurrence (p=0.0001) in both groups during the follow-up period (p=0.0001), and OM-89 was as effective in preventing recurrence as nitrofurantoin.[34]

In a second RCT, 38 children (age range 3–13) who had 2–3 UTIs in the previous 6 months were enrolled. All patients received both antibiotic treatment with either amoxicillin/clavulanate or second/third-generation cephalosporins, and either OM-89 prophylaxis or placebo for 3 months. Participants were followed for 3 months post-treatment and the occurrence of UTI, bacteriuria, and level of secretory IgA (sIgA) in the urine were recorded. 92% of participants treated with OM-89 experienced no recurrence compared with 46% in the control group. sIgA, a potential marker for UTI predisposition, was low in all patients at the beginning of the study; however, by 6 months 72% of OM-89 treated participants showed asignificant increase (65%) in sIgA (p=0.02), correlating with the reduction in recurrences. In 68% of OM-89 patients, urine was sterile after 6 months.[35]

Summary

Accurate diagnosis is key in the care of children with UTI. Following treatment with antibiotics, assessment and treatment of underlying conditions that contribute to recurrence of UTI is essential for a successful resolution. Immunostimulant therapies, such as OM-89, appear to be well tolerated and promising in preventing recurrence, and vaccination shows some promise too. Further work is needed on both these prophylactic strategies before firm conclusions can be drawn.

GENITAL PROLAPSE AND URINARY INCONTINENCE: RISK FACTORS FOR UTI

Risk factors for UTI can be divided into two categories: factors that expose the host to potential uropathogens and factors favouring colonisation by uropathogens. In many cases, pelvic floor problems, among the most important of which are prolapse and incontinence, and the interventions used to

treat them, expose women to both categories of risk, resulting in an occult epidemic of rUTI.

Genital Prolapse, Distorted Anatomy, and the Risk of Infection

Even in cases where anatomy is normal, women are at higher risk of colonisation by urinary pathogens than men. Both the shorter length of the female urethra and the short distance between urethral meatus and anus predispose women to UTI, with a distance between urethra and anus of <4.5 cm increasing risk of rUTI.[36] Factors such as child birth, surgery, and anatomical issues (e.g. prolapse) can shorten urethral–anal distance further. In a typical example of urethral prolapse, angling of the urethra can result in the urethra and anus coming into close contact. Other conditions such as perineal tears or extensive genital hiatus can also shorten the urethral–anal distance and make infections more likely.[37] Many conditions, such as the altering of vesicourethral angle during prolapse and urolithiasis (urinary stones), can lead to obstruction of urinary flow and urinary stasis. That urinary stasis predisposes a patient to UTI is one of the axioms of urology, since it aids bacterial adhesion and multiplication.[38] Urethral diverticulum, the formation of small pouches along the urethra, though not strictly a dysfunction of the pelvic floor, also results in urinary stasis. rUTI is reported in 30% of women with urethral diverticulum, a condition that also predisposes to urolithiasis, another UTI risk factor.

Incontinence and the Risk of UTI

Untreated urinary incontinence increases perineal moisture, creating an environment suitable for increased bacterial growth. The use of sanitary pads in these patients may also increase the risk of UTI. Incontinence is a common problem in residential care where cognitive and functional impairment and the high rate of other comorbidities can lead to reduced hygiene, elevated post-voiding residuals, and greater need for catheterisation, thus increasing rates of UTI. Elderly institutionalised women experience UTI more frequently (50%) compared with those who are not institutionalised (25%).[39,40]

Treatment-Related Risk Factors

As a rule, if genital prolapse is not causing discomfort, persistent infection, or distress, it should not be treated. However, in cases where treatment is required, a pessary is often used. A well-placed pessary will reduce stasis and improve emptying, but equally, if not correctly positioned or of the correct size, it may obstruct urination leading to UTI. Placement of a pessary may also cause a discharge (bacterial vaginosis) facilitating the growth of *Escherichia coli*. In patients who place their own pessary, incorrect placement further increases the risk of colonisation from the anus to the perineum. Undergoing surgery of any kind greatly increases the risk of a UTI, especially if it involves the manipulation of the urinary tract and catheter placement. A patient's average risk of developing UTI within 30 days post-surgery is 1.7%, varying with type of surgery: colorectal 2.6%; perineal resections 5.6%; and anti-incontinence surgeries 10–32%. Anti-incontinence surgery is now a common intervention. In cases where incontinent patients also suffer from rUTI, surgery may reduce recurrence. However, as stated above, the surgery itself also increases incidence of UTI. In a study of 1,356 women (>65 years) who underwent placement of sub-urethral slings (standard surgery), one-third reported UTI within 3 months of surgery and almost 50% reported UTI within 1 year.[41] In cases of severe incontinence, a urethral catheterisation may be necessary. In many cases, catheter placement introduces bacteria into the bladder and the catheter may also aid colonisation. The risk of UTI in catheterised patients is increased especially in patients with an indwelling catheter or long-term catheterisation, as further explored in the following section.[42]

Summary

Both the pathology and treatment of urogynaecological abnormalities contribute to UTI risk and more work is required to investigate epidemiology and disease burden in this patient group. It is likely that the putative occult epidemic of UTIs in patients with urogynaecological abnormalities represents an area of substantial unmet clinical need.

INTERSTITIAL CYSTITIS (IC): A LINK WITH rUTI?

IC is a disease of the urinary bladder characterised by frequency and urgency; urinary incontinence; and pelvic pain, with pain being the key symptom. Accurate epidemiological analysis of IC is hampered by the lack of a widely accepted definition; however, prevalence has been estimated at 18.1/100,000 in women and 10.6/100,000 in both sexes.[43] Patients with IC usually present at

the age of 20 years and estimated prevalence at age 40 is 3.8%.[44] Signs and symptoms include: bladder pain or discomfort that increases with filling and may diminish with voiding; urinary frequency ranging from 10–50 times per 24 hours; urgency caused by increasing pain and nocturia. These symptoms range in severity and may be intermittent or constant.[45-47]

A putative aetiological link exists between rUTI and IC. The precise aetiology of IC remains to be elucidated; however, recurrent bladder insults due to numerous conditions, including cystitis, may be a contributory factor in disease onset. Consequent damage to uroepithelial cells and dysfunctional repair mechanisms are thought to result in leaking of urine constituents, such as potassium, into the interstitium, resulting in a cascade of downstream processes, which may result in chronic neuropathic pain.[46] The putative link with rUTI and the concomitant role for prophylaxis should be considered for future research.

INDWELLING CATHETERS: INFECTION PREVALENCE AND REDUCTION

Urethral catheterisation is a common procedure required by 15–25% of patients in general hospitals and nursing homes. It is also the leading cause (65–75%) of hospital-acquired UTIs (HAUTI).[48,49] The potential for serious morbidity in patients with catheter-associated HAUTI should not be underestimated, with mortality rates up to three-times higher than in catheterised patients without a UTI (level of evidence [LoE] IIB).[50]

Incidence and Pathogenesis of Catheter-Associated Bacteriuria (CAB) and UTI

The incidence of bacteriuria increases 3–8% per day following insertion of a urethral catheter.[51,52] The 100% infection rate 1 month post-insertion is a striking illustration of the risk associated with long-term catheterisation. Indeed, the duration of catheterisation is the most important risk factor in catheter-associated UTI (CAUTI). Other risk factors include diabetes mellitus, increased serum creatinine, female gender, absence of concomitant antibiotic use, indications other than surgery, errors in catheter care, and microbial colonisation of the drainage bag (LoE IIa–III).[53-55] 20% of patients will be colonised immediately upon catheterisation (LoE IIa).[50,51] Following insertion, patients will continue to be at risk of colonisation though intraluminal routes, including bacteria ascending through the lumen of the catheter and reflux of urine from contaminated bags, and extra luminal routes such as ascension on the extraluminal surface of the catheter from the urethra. The formation of biofilms results in a favourable environment for colonisation via the extraluminal route.[56]

Prevention of CAUTIs

Currently, there are three international guidelines aimed at reducing CAUTI,[57-59] and three tranches of preventive measures exist, addressing indwelling urethral catheterisation, bacteriuria, and bacteriuria-related complications.

Prevention of catheterisation

The most effective form of primary prevention for CAUTI is to avoid catheterisation. Data suggest that approximately 30% of initial catheterisations are unnecessary (LoE IIaB).[53,60,61] Reducing unnecessary catheterisation should be the first step towards prevention of CAUTI. Institutional staff education and reminder systems for physicians and nurses should be introduced to avoid unnecessary catheterisation.[61] Where catheterisation is necessary, intermittent catheterisation should be used as an alternative to short (LoE Ia) and long-term indwelling catheterisation.[62,63] Suprapubic catheterisation, involving the placement of a drainage tube into the bladder through an incision in the skin (LoE III),[57,59] should be considered for both short and long-term catheterisation.[51] Data concerning whether suprapubic catheterisation can significantly reduce CAUTI are insufficient. However, according to a 1991 meta-analysis, suprapubic catheterisation reduces CAB, discomfort, and re-catheterisation rates.[52]

Prevention of CAB

Reducing the duration of catheterisation is likely to be the most effective method for preventing bacteriuria. In a prospective study of medical and intensive care inpatients, up to 47% of 912 patient-days of catheterisation were unjustified.[54] Use of aseptic technique when inserting catheters aids bacteriuria prevention. There is some controversy regarding the use of clean versus sterile technique in reducing CAUTI. Data from a RCT suggest there is no effect on the rate of CAB or CAUTI (LoE Ib).[64] However, the Center for Disease Control guidelines recommend using aseptic technique and sterile equipment in the acute-care setting (LoE IB).[58] Use of a closed system is also effective in reducing CAB (LoE IIa), with a 50% incidence

of asymptomatic CAB at 14 days in a closed system versus 95% at 96 hours in an open system.[65,66] A meta-analysis showed that the use of catheters coated with antimicrobial agents reduced CAB and CAUTI in short-term catheterised patients, especially in the intensive care setting (LoE IIa–III).[67] Silicone-coated catheters are resistant to bacterial adherence, but in a study on *Proteus mirabilis*-infected urine, no catheter prevented blockage after 56 hours.[68] Heparin-coating of catheters reduces bacterial incrustation *in vitro* and *in vivo*, likely due to its strong electronegativity.[69–71] Similarly, coating with phosphoryl-choline reduced encrustation in urethral stents.[72] A novel approach using surface acoustic waves has recently been demonstrated to disrupt biofilm formation efficiently *in vivo*,[73] and may also reduce CAUTI in patients with indwelling catheters.[74]

Prevention of CAUTI complications

Secondary preventive measures, aimed at halting infection progression and complications, include antimicrobial prophylaxis and screening for ASB followed by treatment. Screening and treatment of asymptomatic CAB is not recommended due to lack of treatment benefit. Systemic antimicrobial treatment for asymptomatic CAB is only recommended in patients undergoing urological surgery or implantation of prostheses (LoE A), if treatment is part of a plan to control nosocomial infection due to a virulent organism (LoE B), in patients who have a high risk of serious infectious complications (LoE C), in pregnancy (LoE B), and in infections caused by strains causing a high incidence of bacteraemia (LoE B).

A meta-analysis on short-term catheterisation did not recommend routine antibiotic prophylaxis. However, authors concluded that antibiotic prophylaxis is effective in some postoperative settings.[62] In light of the above evidence, antibiotic prophylaxis should be routinely used only in patients at high risk of serious complications associated with UTIs (e.g. granulocytopaenia or recent urological/gynaecological surgery). Data on other prophylactics tend to be negative or inconclusive. Methenamine salts should not be used routinely (LoE C). Data on cranberry-based prophylaxis are insufficient (LoE D), and data on ascorbic acid are contradictory. Irrigation with antiseptics, such as povidone-iodine/chlorhexidine, or antibiotics is ineffective in most patients. Some catheterised spinal cord injury (SCI) patients have been successfully treated with OM-89.[75]

Summary

Patients with indwelling urinary catheters are at increased risk of UTI. Currently, the most effective methods of prevention of CAUTI appear to involve reduction of catheter use. Technological efforts to improve catheter design, or target adhesion with novel sonic methods show some promise.

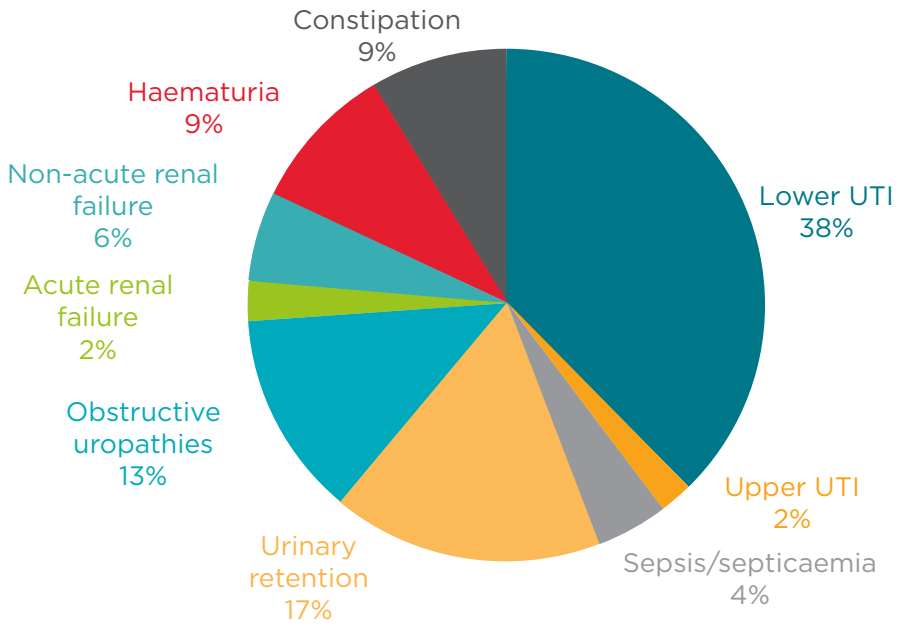

Figure 1: Co-morbidities associated with neurogenic bladder syndrome.[82]
UTI: urinary tract infection.

Current prophylactic measures are lacking in broad efficacy and more research into alternative compounds is required.

NBD: PREVENTING RECURRENT SYMPTOMATIC UTI

NBD can be caused by a range of conditions categorised by the region of the nervous system affected: brain; supra-sacral spinal; and sacral spinal or peripheral nerve.[76] Bladder function is controlled through a complex balance of sympathetic, somatic, and parasympathetic innervation. Imbalances in neuronal activity between these systems may cause overactivity syndromes such as detrusor sphincter dyssynergia. In this condition, coordination between detrusor and sphincter is impaired during voiding, resulting in an inability to void urine. Detrusor sphincter dyssynergia is associated with recurrent episodes of UTI as well as more serious long-term damage to the urinary tract.[77] Despite some similarities, this condition is distinguished from atonic bladder/incontinence caused by peripheral nerve injury.

Lesions affecting caudal sections of the spinal cord (sacral segments s2–s4) result in bladder and kidney dysfunction due to parasympathetic and somatic disruption. It is worth noting that in individuals with this type of lesion, the function of the majority of internal organs remains intact due to vagal innervation.[78] UTI is one of the most common complications in SCI, traumatic brain injury, and stroke.[79-81] Lower UTI is the most common medical complication of patients with NBD (annual incidence 31.3%); however more serious conditions, including sepsis/septicaemia (annual incidence 3.7%) and acute renal failure (annual incidence 4.6%), are not uncommon in this cohort (Figure 1).[82] Currently, there is a lack of robust evidence on the incidence of rUTI in NBD, with the majority of the literature focused on SCI.

rUTIs in SCI-Associated NBD: Incidence and Risk Factors

Both the location and severity of SCI affect prognosis and bladder management. Levels of injury include tetraplegia, affecting the arms, trunk, and legs, and paraplegia, affecting the trunk and/or legs; whereas severity can be complete, resulting in no motor or sensory function below the level of injury, or incomplete, with some preserved function. Bladder management requires dexterity and hand function meaning that paraplegic and tetraplegic patients require different management. Current guidelines recognise the complexity of bladder management in this population and leave significant room for interpretation.[76]

Predicting prognosis is difficult in the early stages following spinal injury; in general there will be efforts to transition bladder management from indwelling catheterisation to an intermittent regimen, where possible. The importance of the transition to an intermittent regime is illustrated in one of the few papers addressing the epidemiology of NBD in hospitalised patients with SCI. As expected, UTI rates are significantly higher in patients with indwelling catheters (2.72 episodes/100 person-days, OR [CI] 7.77 [5.8–10.4]) compared with clean intermittent catheterisation (0.41 episodes/100 person-days, OR [CI] 0.42 [0.31–0.58]).[83] Overall, patients with SCI suffered 2.5 episodes of UTI per year. The relation of this UTI rate to SCI patients in the wider community is unknown.

Alongside catheterisation, risk factors for rUTI in SCI include level of functional independence, presence of vesicourethral reflux, and duration of NBD. The exact profile of true risk factors is still unclear due to the frequent concurrence of catheterisation and reduced functional independence in tetraplegic individuals, as well as the effect of reduced sympathetic innervation of the spleen on the immune system.[83] From the perspective of UTI diagnosis, lack of sensory input means that patients may be unaware of typical symptoms, such as dysuria and urgency. As a result, defining and diagnosing a symptomatic UTI is challenging.

rUTI Prophylaxis in SCI-Associated NBD: a Critical Appraisal of the Literature

A systematic search of the literature conducted by our research group, which was aimed at collecting the needed data to design a pilot study in this patient population, revealed five RCTs focused on prophylaxis of symptomatic rUTI in NBD.[84-88] A range of definitions of symptomatic UTI were used and a range of interventions were investigated including the antibiotics nitrofurantoin and ciprofloxacin,[79,80] probiotics using non-virulent *E. coli* strains 83972 and HU2117,[86,87] and the use of hydrophilic catheters.[88] There was variability in the quality of reporting between studies, with validity of the results of the two earliest papers compromised by lack of reporting of group size and duration of follow-up.[84,85] There were also issues

of comparability between trials due to variability in outcome measures used.[84-88]

The aforementioned difficulty in defining symptomatic UTI in SCI patients, with apparently no consensus in definitions used between the trials, is also a factor in interpreting outcomes from these papers that may lead to wrong conclusions.[84-88] The definitions used in the two trials by Darouiche and co-workers,[86,87] combining evidence of bacteriuria, immune system activation (pyuria and fever), and a list of signs and symptoms designed to circumvent sensory loss (suprapubic or flank discomfort, bladder spasm, increased spasticity, and worsening dysreflexia), offer an encouraging approach. Results from the two antibiotic trials were mixed. No efficacy in rUTI reduction was reported by the nitrofurantoin trial.[84] Prophylaxis with ciprofloxacin reportedly prevents rUTI; however, the validity of this result is questionable as previously stated.[85] It is worth noting that due to the problem of antibiotic resistance, guidelines do not recommend routine antibiotic prophylaxis, except in patients with a recent history of severe UTI.[76] Use of a hydrophilic catheter did not reduce the rate of rUTI, but did reduce the rate of treated UTI, although the lack of a defined primary outcome in this trial is of concern.[88] Despite methodological issues regarding group allocation and difficulties with inoculation of patients, the results from the two probiotic trials, both reporting a reduction in rUTI, show some promise.[86,87]

OM-89 for the Treatment of rUTIs in SCI-Associated NBD

One double-blind, placebo-controlled, crossover study exists, investigating the efficacy of the oral immunostimulant OM-89 for the treatment of bacteriuria in paraplegic (n=49) and tetraplegic (n=18) patients with NBD.[75] The study groups were well balanced with regard to the level of injury and aetiology of NBD, and all patients were managed with intermittent catheterisation. Symptomatic rUTIs were not assessed. OM-89 treatment resulted in a reduction in bacteriuria incidence (≥10^4 CFU/mL per treatment period). This reduction continued in the treatment group following crossover, suggesting a long-term protective effect likely mediated by boosting of host defences (Figure 2). OM-89 had an antibiotic sparing effect and was well tolerated (9.4% versus 9.1% adverse events, OM-89 and placebo, respectively).

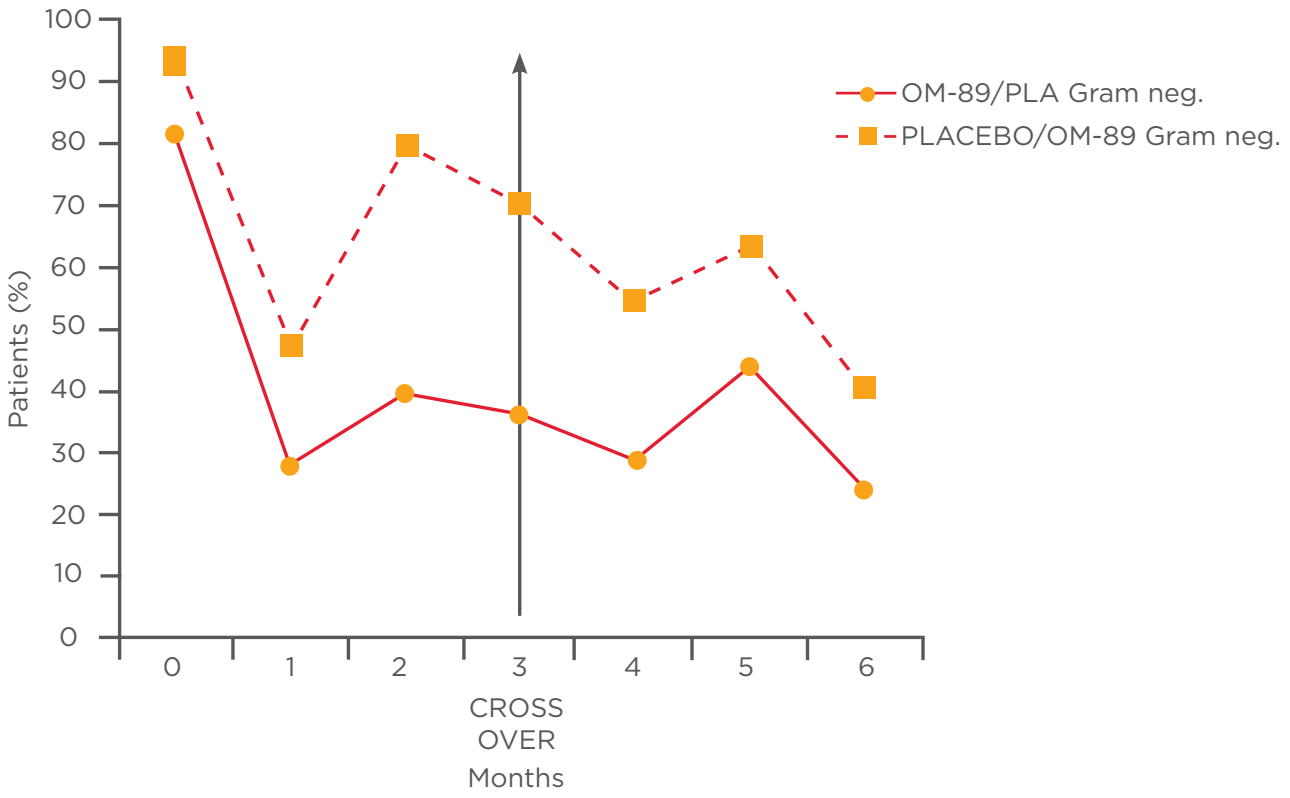

Figure 2: Percentage of patients with Gram-negative bacteriuria of ≥10^4 CFU/mL per treatment period.[75]
CFU: colony-forming units; PLA: phospholipase A.

Summary

Despite limited epidemiological data, it is clear that rUTI represents a major burden in NBD patients. Current guidelines for NBD leave a great deal of room for individual interpretation. However, regulatory bodies recognise the need for more research in novel treatment approaches for infectious disease.[89] Investigating UTIs in a complex NBD population is a very challenging task, an issue underlined by the limited number of RCTs investigating prophylaxis in this group and the methodological issues therein. Future research must be built upon an evidence-based definition of symptomatic UTI in NBD and robust methodology in a larger sample size if progress is to be made in relieving the burden of rUTI in individuals with NBD.

CONCLUSION

The above conditions are diverse in nature with each having a unique set of factors predisposing to increased risk of UTI. High-quality data are particularly sparse with regard to prophylactic measures which may reduce rUTI in the above groups, many of which represent high-risk groups for significant morbidity related to UTI. These pathological conditions are united in a need for an increase in research focused on reducing the prevalence and recurrence rate of UTI with different promising management studies.

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