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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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 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. 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.

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. 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).

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.

### Table 1: Gram-negative resistance mechanisms and their antibiotic consequences

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Antibiotics affected</th>
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<tbody>
<tr>
<td>Loss of porins</td>
<td>Carbapenems (e.g. imipenem)</td>
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<tr>
<td>β-lactamases</td>
<td>β-lactams (including carbapenems for some β-lactamases)</td>
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<tr>
<td>Increased expression of efflux pumps</td>
<td>β-lactams (e.g. meropenem), fluoroquinolones, aminoglycosides, tetracyclines (e.g. tigecycline), chloramphenicol</td>
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<tr>
<td>Antibiotic modification enzymes</td>
<td>Aminoglycosides, ciprofloxacin</td>
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<tr>
<td>Target-site modification enzymes</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Ribosomal mutations</td>
<td>Tetracyclines, aminoglycosides</td>
</tr>
<tr>
<td>Metabolic bypass (use of alternate, uninhibited enzymes)</td>
<td>Trimethoprim, sulphonamides</td>
</tr>
<tr>
<td>Lipopolysaccharide mutations</td>
<td>Polymyxins</td>
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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. Data from TEST (Tigecycline Evaluation and Surveillance Trial), 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. Data from 2005-2007 showed more than one-fifth of E. coli in Latin America were ESBL producers. In a 2006 Brazilian study, 57.1% of these ESBL-positive bacteria were also resistant to second-generation fluoroquinolones (ciprofloxacin). 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. 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. 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). Other studies have reported a mortality rate of around one in three. 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. 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. 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). 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

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

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</tr>
</thead>
<tbody>
<tr>
<td>1. Fosfomycin</td>
<td>97.2</td>
<td>99.0</td>
<td>97.9</td>
<td>99.3</td>
<td>97.9</td>
<td>97.0</td>
<td>98.8</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2. Mecillinam</td>
<td>94.1</td>
<td>97.0</td>
<td>97.5</td>
<td>97.3</td>
<td>94.1</td>
<td>94.6</td>
<td>97.7</td>
<td>100</td>
<td>96.5</td>
<td>96.1</td>
</tr>
<tr>
<td>3. Nitrofurantoin</td>
<td>94.1</td>
<td>97.3</td>
<td>92.5</td>
<td>94.7</td>
<td>97.4</td>
<td>94.3</td>
<td>92.2</td>
<td>100</td>
<td>100</td>
<td>98.0</td>
</tr>
<tr>
<td>4. Ciprofloxacin</td>
<td>88.1</td>
<td>98.2</td>
<td>95.4</td>
<td>87.4</td>
<td>87.0</td>
<td>89.2</td>
<td>92.2</td>
<td>98.3</td>
<td>96.5</td>
<td>92.3</td>
</tr>
<tr>
<td>5. Nalidixic acid</td>
<td>73.5</td>
<td>93.6</td>
<td>90.5</td>
<td>82.7</td>
<td>73.6</td>
<td>75.4</td>
<td>84.4</td>
<td>91.9</td>
<td>93.1</td>
<td>67.3</td>
</tr>
<tr>
<td>6. Amoxi/clav</td>
<td>77.3</td>
<td>90.9</td>
<td>88.8</td>
<td>83.0</td>
<td>71.9</td>
<td>79.8</td>
<td>85.5</td>
<td>93.5</td>
<td>82.8</td>
<td>51.9</td>
</tr>
<tr>
<td>7. Cefuroxime</td>
<td>75.3</td>
<td>89.2</td>
<td>91.3</td>
<td>83.4</td>
<td>78.2</td>
<td>74.5</td>
<td>77.7</td>
<td>77.4</td>
<td>89.6</td>
<td>75.0</td>
</tr>
<tr>
<td>8. TMP-SMX</td>
<td>66.2</td>
<td>87.7</td>
<td>74.0</td>
<td>69.4</td>
<td>71.1</td>
<td>54.4</td>
<td>80.0</td>
<td>70.9</td>
<td>79.3</td>
<td>59.6</td>
</tr>
<tr>
<td>9. Ampicillin</td>
<td>35.3</td>
<td>60.8</td>
<td>59.2</td>
<td>42.0</td>
<td>43.0</td>
<td>34.7</td>
<td>40.0</td>
<td>43.5</td>
<td>65.5</td>
<td>32.6</td>
</tr>
</tbody>
</table>

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

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

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%. 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. 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 geographic regions. CoNS: coagulase negative staphylococci.
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. 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%).

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.

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). Rates were extremely high in this data set. MDR in the *Enterobacteriaceae* as a whole had a prevalence of 51% and XDR of 32%.

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.

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. 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. The international European Association of Urology (EAU) guidelines are close behind with five recognised UC categories. 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.

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. 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 their exclusive use in uncomplicated UTI and consequent reduction in collateral damage.

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.

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Figure 2: Treatment algorithm of recurrent urinary tract infection.
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). In a pilot 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). More data are needed and a number of trials are ongoing (ClinicalTrials.gov). It may be that the use of anti-inflammatory agents 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. 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. However, in patients with complicated conditions, including spinal-cord injury patients, diabetes mellitus, and catheterisation, no benefit in treating ASB has been found.

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. 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. Guidelines in Latin America

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. 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.
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).

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. 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.

**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 recognize 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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