

## Editorial

# Recurrent Urinary Tract Infection in the Gynecologic Practice: Time for Reviewing Concepts and Management

## *Infecção do trato urinário recorrente na prática ginecológica: momento de rever conceitos e conduta*

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An independent panel of physicians with expert interest in urinary tract infection (UTI), including gynecologists, urologists, molecular biologists, infectologists, immunologists and epidemiologists met in a forum in Panama (Foro en Infecciones Urinarias Recurrentes - FIUR) to review diagnosis and treatment recommendations for the empiric therapy of uncomplicated UTIs taking into account antibiotic resistance and considering the use of guidelines to promote an optimal practice for recurrent urinary tract infections (RUTIs).

Urinary tract infections are among the most common bacterial infections, and are a frequent complaint of women visiting their gynecologists. The accurate diagnosis and treatment of UTIs play an important role in cost-effective medical care and appropriate antimicrobial utilization.<sup>1</sup> Antimicrobial resistance is a global issue, and concerns have been raised that some infections for which therapy is now available might become untreatable.<sup>2</sup> The widespread empiric use of antibiotics, while convenient, potentially contributes to the development of antimicrobial resistance.<sup>2</sup>

The evolution of antimicrobial resistance in community-acquired *Escherichia coli*, however, requires a constant reevaluation of the empiric antimicrobial therapy.<sup>2</sup> The variables to be considered in selecting an antimicrobial drug include efficacy, adverse effects, cost, and potential for future resistance.<sup>2</sup> Practitioners always need to balance the antimicrobial selection for an optimal patient outcome

with the potential for contributing to further antimicrobial resistance through widespread empiric use. Overly long or improper treatment regimens may also lead to drug resistance.

### Asymptomatic Bacteriuria Should Not Be Treated in the General Population

Urinary tract infection is not a laboratory-defined diagnosis. Diagnosis should be based on clinical symptoms whenever possible, and confirmed by positive urine microscopy and culture.<sup>1</sup> Quantitative colony counts should not be used to guide therapy in asymptomatic patients. In symptomatic women, colony counts of > 100,000 colony-forming units/ml are usually clinically relevant.

The frequent over diagnosis of UTI and the subsequent treatment are common problems. A considerable amount of bacteria found in the urine without association with any clinical symptoms is defined as asymptomatic bacteriuria. There are many myths that have been maintained on the interpretation of patient symptoms and laboratory results that lead to the overtreatment of asymptomatic bacteriuria.<sup>1</sup>

Urine color and clarity or odor should not be used alone to diagnose or start antibiotic therapy in any patient population.<sup>1</sup> There is also a wide variation in the interpretation of urinalyses among different providers. The presence of bacteria in the urine on microscopic examination or by positive

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culture without UTI symptoms is not an indication of a UTI due to the possibility of contamination and asymptomatic bacteriuria. Pyuria, leukocyte esterase, or nitrate, individually or accompanying asymptomatic bacteriuria, are also not necessarily an indication for antimicrobial treatment in the general population. Some exceptions include: pregnancy and any urologic procedure with bleeding, such as urinary tract stenting.<sup>1</sup> Recent evidence suggests that in younger women with RUTI that bacteriuria may be “protective” for future UTIs with more pathogenic organisms.<sup>1</sup> Unnecessary treatment with antibiotics can also increase the resistance of the bacteria that cause UTIs, making antibiotics less effective for future use.

### **A Three-Day Course of Antibiotics is Adequate in Most Non-Pregnant Women with Uncomplicated Lower UTIs**

For the treatment of uncomplicated UTIs, narrow-spectrum antimicrobials are appropriate, given the consistent bacteriology, and are preferred, given concerns about antimicrobial resistance. Three days of antibiotic therapy is similar to 5–10 days in achieving symptomatic cure during uncomplicated UTI treatment in most women who are not pregnant. Short-course regimens (3 to 5 days) are usually effective in eradicating asymptomatic bacteriuria and decreasing the occurrence of UTIs during pregnancy.<sup>3</sup> Adverse effects are significantly more common in the 5–10-day treatment. Therefore, longer courses may be considered in pyelonephritis or complicated UTIs.<sup>4</sup>

### **Fuoroquinolones Should Not Be Considered as a First-Line Treatment**

In Brazil, gynecologists have altered their approach to first-line therapy for uncomplicated UTIs. Trimethoprim-sulfamethoxazole prescriptions for uncomplicated UTIs have declined, while fluoroquinolone prescriptions have increased.<sup>2</sup> Fluoroquinolones, including norfloxacin, ciprofloxacin, ofloxacin and levofloxacin, are effective as 3-day therapy, and are well tolerated. However, increasing antimicrobial resistance to fluoroquinolones is being observed worldwide, and it reaches almost 20% in uncomplicated UTIs. Therefore, fluoroquinolones should not be considered as a first-line therapy for UTIs.<sup>2</sup>

### **Antibiotics Should Be the Third Measure in the Prophylaxis of RUTIs**

Recurrent urinary tract infections are defined as having three or more symptomatic UTI episodes per year, or two or more UTIs within 6 months. Mostly young but also postmenopausal women are affected by this condition. Approximately 20 to 30% of women with a UTI have a recurrence.<sup>5</sup> According to the 2015 European Association of Urology guidelines and to the 2015 Febrasgo Manual of Urogynecology,<sup>6</sup> behavioral change to avoid risk factors is the first measure in the prophylaxis of RUTI episodes. The

behavioral measures include appropriate fluid intake, avoiding the use of spermicide in premenopausal women, and the treatment of genital atrophy with local estrogen.<sup>6</sup> This approach can lower the recurrence rate by ~ 30%. Non-antimicrobial measures come second, and antibiotic prophylaxis should be considered the third measure to avoid adverse events and the collateral damage of unnecessary long-term antibiotic use.<sup>6,7</sup> Self-diagnosis and self-treatment of recurrences is reliable in premenopausal and postmenopausal women with RUTIs.<sup>8</sup> Genitourinary symptoms are not necessarily related to UTIs, and are not necessarily an indication for antimicrobial treatment in postmenopausal women.

The current guidelines of the American College of Obstetricians and Gynecologists recommend continuous once-daily prophylaxis with nitrofurantoin, norfloxacin, ciprofloxacin, trimethoprim, trimethoprim-sulfamethoxazole, levofloxacin, gatifloxacin, or fosfomycin tromethamine for 6 to 12 months.<sup>9</sup> The increasing resistance rates of *Escherichia coli* to antimicrobial agents has, however, stimulated the development of new strategies involving non-antimicrobial compounds for the prevention of UTIs.<sup>8</sup>

### **Non-Antimicrobial Methods Should Be Considered for RUTI Prevention**

Non-antimicrobial options include cranberry products and *Lactobacillus crispatus* intravaginal suppositories in premenopausal women, and, in postmenopausal women, options include topical estrogen, oral capsules with *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14.<sup>8</sup> Estrogen stimulates the proliferation of vaginal lactobacilli, reduces the vaginal pH from  $5.5 \pm 0.7$  to  $3.6 \pm 1.0$ , and prevents vaginal colonization of Enterobacteriaceae, lowering the occurrence of new episodes of UTI.<sup>6</sup> Oral estrogen has no effect on RUTIs, and should not be prescribed for their prevention.<sup>8</sup> However, local estrogen is effective in decreasing the recurrence rate, especially in postmenopausal women. The efficacy, safety and tolerability of this approach has not been compared directly with antimicrobial prophylaxis, but both strategies appear to be effective in postmenopausal women.<sup>5,6</sup>

Cranberries have been used widely for several decades for the prevention and treatment of UTIs. There is a variety of cranberry products on the market, and the optimal intake for the “active” ingredient to be effective in RUTIs prevention is still unknown.<sup>8,10</sup> Compared with placebo, water or no treatment, cranberry products did not significantly reduce the occurrence of symptomatic UTIs overall. The effectiveness of cranberries was also not significantly different compared with antibiotics for women.<sup>10</sup> Therefore, cranberry products cannot currently be recommended for the prevention of UTIs.<sup>10</sup>

There are new promising strategies on the horizon for RUTI management, which are prophylaxis with bacterial extracts, such as the oral immunostimulant OM-89, or the vaginal vaccine Urovac.<sup>8</sup> Immunoactive prophylaxis of recurrent UTIs with lyophilized lysate of *E. coli* (OM-89) has been shown to be more effective than placebo in randomized trials with a good safety profile.<sup>11,12</sup> It is recommended for

RUTI prevention by the 2015 European Association of Urology guidelines and the 2015 Febrasgo Manual of Urogynecology.<sup>6,7</sup> The accessibility of clinically proven probiotics for UTI prophylaxis is currently not universal. Other promising modalities need to be tested in further controlled trials to prove their preventive benefit.<sup>5</sup>

## Final Considerations

Gynecologists frequently evaluate patients for UTIs. Some misperceptions of the interpretation of patient symptoms and laboratory results lead to UTI overtreatment. Developing simple decision rules, diagnostic guidelines or other educational interventions may minimize the unnecessary use of tests and antibiotic treatments. Recurrent urinary tract infections are common, and it is important that they are managed and prevented effectively. The increasing resistance rate of *Escherichia coli* to antimicrobial agents has, however, stimulated interest in non-antibiotic methods for the prevention of UTIs. Among the different forms of immunoprophylaxis studied, the oral immunostimulant OM-89 seems the most promising to prevent RUTIs.

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