Tratamento e Profilaxia da Cistite Recorrente na Mulher Não Grávida

Management of Recurrent Cystitis in the Non-pregnant Women

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Resumo

Introdução: A cistite é uma das doenças infeciosas bacterianas mais frequentes no mundo inteiro, especialmente na população feminina. Acarreta uma diminuição da sua qualidade de vida, bem como elevados custos médicos. Para além disso, até um terço de todas as mulheres que já tiveram um episódio de cistite têm, pelo menos, uma recorrência desta patologia durante a sua vida.

Objetivo: Esta revisão pretende fazer uma análise dos fatores de risco mais importantes que contribuem para o desenvolvimento de cistites recorrentes, assim como do tratamento e da profilaxia desta condição médica.

Métodos: Realizou-se uma revisão na base de dados da PubMed com os seguintes termos: recurrent UTI in women; prophylactic antimicrobials for recurrent cystitis; prophylaxis of cystitis in women; Escherichia Coli virulence factors; host pathogenesis in recurrent urinary tract infections; e treatment of urinary tract infections in women.

Resultados: A antibioterapia é essencial no tratamento da cistite aguda não complicada. No entanto, esta não é obrigatória no que toca à prevenção de infeções futuras do trato urinário, já que existem outras opções. O consumo de arando, a administração intravaginal de *Lactobacillus*, a aplicação vaginal de estradiol/estriol, extrato de *E. Coli* e a instilação intravesical de ácido hialurónico e sulfato de condroitina são alternativas eficientes e seguras para a prevenção de infeções urinárias recorrentes. Os antagonistas da FimH ainda se encontram sob estudo mas são possíveis armas futuras na profilaxia da cistite. A profilaxia antibiótica na prevenção da cistite recorrente, é muito eficaz, mas o seu uso deve ter em consideração os efeitos adversos e sobretudo o crescente problema mundial da resistência aos antibióticos. São possíveis várias abordagens, sendo que os esquemas preferidos são profilaxia continua, pós-coito ou intermitente.

Conclusões: Assim, pode-se concluir que, em relação ao tratamento de uma infeção do trato urinário aguda, é preferível recorrer à antibioterapia. No entanto, quando se pretende prevenir a recorrência futura destas infeções existem várias opções para além do uso de antibióticos, que não acarretam os seus efeitos adversos. Muitas destas alternativas ainda necessitam de estudos mais aprofundados mas os realizados até agora mostram que são eficazes e seguras.

Palavras-chave: Cistite, mulheres, profilaxia antibiótica, terapêutica preventiva.

Abstract

Introduction: *Cystitis is one of the most prevalent infectious diseases worldwide, especially among women, causing a reduction in their quality of life and increasing medical costs. Furthermore, up to one third of all women who have experienced an episode of cystitis, have recurrent urinary tract infections during their lifetime.*

Objective: *The aim of this review was to analyze the risk factors that contribute to the development of recurrent urinary tract infections, as well as management and prophylactic therapies for this condition.*

Methods: *We have conducted a review on PubMed database, regarding the following subjects: recurrent UTI in women; prophylactic antimicrobials for recurrent cystitis; prophylaxis of cystitis in women; Escherichia Coli virulence factors; host pathogenesis in recurrent urinary tract infections; and treatment of urinary tract infections in women.*

Results: *Antibiotic therapy is essential to the therapeutic strategy for acute uncomplicated cystitis. However, for prevention of future urinary tract infections antibiotic therapy is not mandatory, since there are valid alternative ways. Cranberry intake, administration of intravaginal Lactobacillus or vaginal application of estriol/estradiol, E. Coli extract and intravesical instillation of hyaluronic acid and chondroitin sulphate have proved to be safe and efficient in preventing recurrent cystitis. FimH antagonists, still under study, may also become a legitimate weapon of prophylaxis. Antibiotic prophylaxis for recurrent cystitis is quite effective. Their use must take in to account adverse effects and mounting worldwide problem of increasing antibiotic resistance. Continuous, post-coital or intermittent self-treatment are the preferred prophylactic schemes.*

Conclusions: *Thus, it can be concluded that to treat an acute urinary tract infection it is preferable to resort to antibiotics. However, to prevent future recurrence of these infections there are several options in addition to antibiotics, which do not cause their adverse effects. Many of these alternatives still require further study, but so far it has been demonstrated that they are effective and safe.*

Keywords: *Cystitis, women, antibiotic prophylaxis, preventive therapy.*

Introduction

Cystitis is defined as a bacterial infection of the lower urinary tract which causes suprapubic pain, urgency and haematuria. Urinary tract infections (UTI) are among the most common bacterial infectious diseases worldwide and account for significant morbidity and high medical costs. Almost half of all women experience at least one UTI during their lifetime, and 20% to 30% of those report one or more recurrences[1]. Recurrent cystitis is defined as, at least, two episodes of UTI in the past 6 months or three episodes in the previous 12 months. Recurrences are caused by persistent focus of infections (relapse) or occur after a successful eradication of the initial infection (reinfection)[1]. Reinfections have been considered to represent the vast majority of recurrent UTI[2]. However, a recent publication seems to indicate that relapse with the same strain may have a prominent role[3].

Escherichia Coli is by far the most predominant uropathogen, causing 80% of acute community-acquired uncomplicated UTI cases, followed by *Staphilococcus Saprophyticus* (10% to 15%), *Enterococcus*, *Klebsiella, Enterobacter* and *Proteus*[4].

Recurrent urinary tract infections (RUTI) affect women of all ages, who can be divided into two main risk groups (premenopausal and postmenopausal women), according to age, hormonal and functional status[5]. Each of these groups has specific risk factors for the development of RUTI, which will be discussed later.

The aim of this review was to analyze the risk factors that contribute to the development of recurrent urinary tract infections, as well as management and prophylactic therapies for this condition.

Methods

A systematic search in the English literature was performed through PubMed in the last year using the following keywords: recurrent UTI in women; prophylactic antimicrobials for recurrent cystitis; prophylaxis of cystitis in women; *Escherichia Coli* virulence factors; host pathogenesis in recurrent urinary tract infections; and treatment of urinary tract infections in women. Published randomized controlled trials, case-control studies and reviews were analyzed. Inclusion criteria were: articles written in English or Portuguese, published in the last 20 years and presented with, at least, the abstract.

Publications were screened by title and, when appropriate, by the abstract. These publications were supplemented by additional publications obtained from their references.

Results

Escherichia coli pathogenesis

· Virulence factors

In healthy women most uropathogens (especially *E. coli*) are originated in the rectal flora and enter the bladder via urethra, with a transitory phase of periurethral and vaginal colonization[2]. *Escherichia coli* is a bacterium that is commonly found in the intestinal tract of humans, but it is known that not all of its strains can cause urinary tract infections, as uropathogenic *E. coli* (UPEC) have specific virulence factors[6]. These virulence factors (VF) include cytotoxins (hemolysins), siderophores, carboxylesterase phenotype and adherence[5]. The most important property is by far the ability to adhere to urothelium (mediated by adhesins located at the bacterial wall in the fimbriae or pili), since this is

understood as the first step in the pathogenesis of UTI[7]. The fimbriae of uropathogenic E.coli are surface glycoprotein projections that express ligands for receptors on uroepithelial cells. The most important are Type 1 fimbriae and P fimbriae[8]. FimH is a crucial subunit of these fimbriae as it mediates both adhesion and cellular invasion to the bladder wall. Furthermore, FimH also allows UPEC to escape the innate immune response through their internalization within urothelial cells[9], and modulates epithelial cells apoptosis and cytoplasmic replication[9]. P fimbriae are generally more associated with cases of acute pyelonephritis[8] and will not be discussed in this review.

Uropathogenic *E. coli* are able to colonize and invade the bladder epithelium, to form intracellular bacterial communities (IBCs) and to establish quiescent intracellular reservoirs. There are still no antibiotics able to eradicate these UPEC reservoirs[3]. All of these characteristics allow *E. coli* to develop RUTI[10].

Host pathogenesis

· Immune and Genetic Factors

There is some evidence suggesting that the existence of a first-degree relative with history of recurrent UTI increases the risk of developing these infections in women, which supports the idea of a genetic influence on defense mechanisms in the urogenital tract[11].

These main defense mechanisms against urinary tract infections include cell-mediated innate responses, in particular through neutrophil reaction[12]. The high incidence of recurrent UTI suggests that many individuals do not develop protective immunity to uropathogens.

Toll like receptors (in particular TLR-4) are sensors of infection that control many aspects of the host immune defense. After uropathogens bind to the urothelial cells, TLR-4 is triggered and a signaling cascade is activated, which leads to the transcription of specific innate immune response genes and the production of inflammatory mediators like IL-6, IL-8 and tumor necrosis factor (TNF)[13]. Thereby, TLR-signaling controls the local activation of cells at the site of infection, as well as the recruitment of inflammatory cells to infected tissues. Ragnarsdottir et al.[14] showed that mice and children not expressing TLR-4 lacked responses to uropathogenic E. coli strains, resulting in development of asymptomatic bacteriuria.

IL-8 (CXCL-8) is involved in neutrophil recruitment and activation, as it binds to the CXCR-1 receptor on the neutrophil membrane. This mediates the migration of uropathogens and neutrophils through the urothelial wall, leading to pyuria[15]. It was recently demonstrated that CXCR-1 polymorphisms can be related with an increased risk of developing RUTI[16].

Vaginal fluid protects against UTI as it consists of cervical mucus and plasma transudate which has antibodies that provide the immune defense against mucosal pathogens. Secretory IgA (S-IgA) is a major component of the immunoglobulins present on mucosal surfaces and has receptors for type 1 fimbriae[17], first referred by Wold et al.[18] Wold et al.[18] also demonstrated that the interaction between Type 1-fimbriae and S-IgA resulted in the inhibition of bacterial adherence to host cells. Therefore, the amount and type of S-IgA present in any individual vaginal fluid could be an indicator of susceptibility to bacterial adherence and subsequent colonization.

· Anatomical factors

Pelvic anatomical characteristics can also play an important role in the pathogenesis of UTI in women. It is known that fecal-perineal-urethral contamination is the most probable explanation for urinary tract infections in women, caused by enteric bacteria. In a case-control study it was determined that the distance from the urethra to the anus was significantly shorter in women with RUTI[19]. Furthermore, the length of the female urethra also facilitates bacteria to ascent in the urinary tract.

· Blood groups

Blood group antigens constitute an important part of the uroepithelial cell membrane and their presence or absence on the surface of these cells may influence individual susceptibility to UTI. Women who secrete their blood type antigens into body fluids and secretions are known as secretors. Non-secretor women have an increased risk of RUTI as their uroepithelial cells show enhanced adherence of uropathogenic *E. coli* compared with secretor women[6]. This occurs because epithelial cells of non-secretor women express unique globo-series glycolipid receptors that bind uropathogenic E. coli[20].

Risk Factors

· Healthy premenopausal women

There are several factors that appear to be related with the development of recurrent UTI in healthy premenopausal women. These include frequency of sexual intercourse in the previous month, spermicide and diaphragm use in the last 12 months, a new sex partner in the previous year, first UTI before 15 years old and a maternal history of UTI[21]. Recent antimicrobial use, which adversely affects vaginal flora, is also highly associated with increased risk of UTI. However, some behaviors were not associated with an increased risk of developing

RUTI, such as pre or post-coital voiding patterns, frequency of urination, delayed voiding habits, wiping patterns, douching and use of hot tubs, frequent use of pantyhose or tights, or body mass index [21].

· Healthy postmenopausal women

The incidence of UTI in women increases with advancing age[6]. Several factors increase the possibility of having recurrent UTI in this population, for example, incontinence, presence of any grade of cystocele, post-voiding residual volume, urogenital surgery and history of UTI in the premenopausal period[22].

Furthermore, the reduced levels of estrogenic hormones present after menopause appear to contribute to the occurrence of recurrent UTI in healthy women. Estrogens stimulate proliferation of *Lactobacillus* in the vaginal epithelium which, as will be discussed later, prevents vaginal colonization by *Enterobacteriaceae*. In addition, the deficiency of estrogens decreases the volume of the vaginal muscles, which will lead to the prolapse of the internal genitalia[23].

In older institutionalized women, the main factors for development of recurrent UTI are deterioration in functional status and urethral catheterization[24].

Management

· Antibiotic treatment

Antibiotic therapy is an important part of the therapeutic strategy for acute uncomplicated cystitis. On the other hand, antibiotic use is related with increased adverse effects and resistance[6], so it is essential to control predisposing factors as far as possible and prevent future infections. The increased antibiotic resistance seen in the last years suggests that the choice of antibiotic should be guided by culture and sensitivity assays. However, an empirical treatment is still considered valid for community-acquired UTI in the absence of complicating factors, as pyelonephritis, chronic infection or atypical symptoms.

Short-course therapy (3 days) is preferred for the management of acute uncomplicated UTI since it is associated with improved patient compliance, lower cost and lower frequency of adverse reactions[25].

During many years, TMP-SMX (trimethoprim-sulfamethoxazole), although not effective against *Pseudomonas* or *Enterococcus*, was considered to be the standard therapy for UTI. However, nowadays it can only be recommended as first-line drug (160/800 mg twice-daily for 3 days) for empirical therapy in communities with rates of uropathogen resistance to TMP under 10-20%[26].

Fluoroquinolones, as ciprofloxacin, fleroxacin, norfloxacin and ofloxacin are effective against most uropathogens and, have the same clinical outcome as TMP-SMX when given as a 3-day regimen. Single-therapy with pefloxacin or rufloxacin is interesting as it may be equivalent to TMP-SMX in the elimination of bacteriuria and its recurrence[27]. However, quinolones have harmful adverse effects and have also showed increased resistance rates. Therefore, they should be only used for more complicated infections, if susceptibility testing is available[28].

Amoxicillin and other β-lactam antimicrobials are more effective when given in a 7-days regimen, which is a disadvantage when compared to 3-days therapies. However, they can be used in pregnant women (if the infecting organism is susceptible) and for infections caused by gram-positive bacteria, such as Group B *Streptococcus*. Pivmecillinam, when available, should also be given twice daily (400 mg) for 7 days, rather than for 3 days[29], and is a good alternative to the treatment of UTI because it has low resistance for *E. coli* and other *Enterobacteriaceae*, without cross-resistance to other antimicrobials used for this purpose[30].

Generally, a 3-day regimen with first- and second-generation oral cephalosporines is not recommended as first-line therapy for uncomplicated UTI[25]. On the contrary, a 3-day course with cefpodoxime-proxetil (third-generation oral cephalosporin) was as safe and effective as TMP-SMX[31].

Some studies have showed that the eradication rate of Fosfomycin Trometamol as a 3 g single-dose was equivalent to other antibiotics. Furthermore, the resistance rate of this therapy for *E. coli* remains very low and shows no cross-resistance to other antimicrobials[32].

Despite the large use of nitrofurantoin for many years, the resistance rate for *E. coli* and *S. Saprophyticus* is still low throughout Europe[32]. A 5-7 day course (100 mg twice daily) is recommended for the use of Nitrofurantoin in acute uncomplicated cystitis. [33] However, this drug is not active against *P. Mirabilis* and *Klebsiella spp.*, which are frequently isolated Gram-negative uropathogens. Nitrofurantoin can be used in pregnant women, children and to prevent recurrent infection, but it has been demonstrated that high doses or long durations of its use may be associated with significant hepatic and pulmonary toxicity[25].

Currently, the first-line choices for empirical treatment of acute uncomplicated UTI in all European countries are single-dose fosfomycin trometamol (3g), pivmecillinam (400 mg) for three days (when available), or nitrofurantoin macrocrystals (100 mg) twice daily for five days[34].

On the other hand, the increasing use of antibiotics is the main reason for emerging resistance strains, so efforts should be made to reduce their use.

Furthermore, some trials have suggested that many cases of uncomplicated UTI are self-limited[35]. Bleidorn et al.[36] study suggested that approximately 66% of patients with UTI symptoms recover or convert to asymptomatic bacteriuria without taking antibiotics. Asymptomatic bacteriuria is common in healthy people and does not need treatment in patients without aggravating factors. Therefore anti-inflammatory agents, as ibuprofen, could be used as first choice therapy for uncomplicated UTI, leaving antibiotics for persisting or recurrent symptoms. However, this approach is controversial and needs more researching.

· Antibiotic prophylaxis

As discussed earlier, it is essential to prevent future urinary infections since they account for increased morbidity and medical costs. In order to do this, one can consider several antibiotic approaches: continuous prophylaxis, post-coital prophylaxis or intermittent self-treatment. All of these methods have been demonstrated to be effective in the management of recurrent uncomplicated UTI. The choice of the most appropriate approach depends on the frequency and pattern of recurrences and willingness of the patient to commit to a specific regimen. The antibiotics most commonly used for this purpose are Nitrofurantoin, Fosfomycin trometamol, TMP-SMX, cephalosporins, and quinolones, all at lower than therapeutic dosages[6]. However, before any prophylaxis regimen is initiated, it is necessary to ensure that a previous UTI is cured, by a negative urine culture one to two weeks after treatment[6].

Continuous prophylaxis maintains an antibiotic barrier in the bladder and has been demonstrated to decrease the number of recurrent episodes of UTI by up to 90%[37]. Nevertheless, it appears that most women return to the earlier pattern of recurrent infections once prophylaxis is stopped. In women who continue to have symptomatic infections, the period of prophylaxis can be extended for 2 or more years. Furthermore, the use of TMP-SMX, for as long as 5 years, has been reported to be effective and well tolerated[24].

A single post-coital dose of antimicrobials may be a more efficient and acceptable method of prevention in women whose infections and symptoms are likely related to sexual intercourse. This treatment regimen usually results in the use of smaller amounts of antimicrobials than continuous prophylaxis, which naturally means less adverse effects[37].

Some women prefer not to take antibiotics over a long period of time and, if they are reliable, they may be candidates for self-treatment with a single-dose or 3-day antimicrobial regimen of TMP-SMX or fluoroquinolone[2], as soon as they feel the first symptoms of cystitis.

In previous studies, it has been demonstrated that all antibiotics commonly used to this purpose have similar prophylactic effect[38].

· Non-antibiotic prophylaxis

The continuous use of antibiotics develops antibiotic-resistant bacterial strains and leads to the impairment of the patient's natural immune defense system. It also alters the vaginal and intestinal flora and induces potentially harmful side effects[4]. Therefore it is essential to find new ways to prevent and treat these infections. Current alternative methods are the use of cranberry juice, probiotic therapy, immunotherapy and intravesical instillation of hyaluronic acid (HA).

Cranberries have been used in the prevention of UTI for many years. The mechanism of action has not been fully understood, however it is known that cranberries contain fructose and type A proanthocyanidins (PAC), which can inhibit *E. coli* type 1 and P fimbriae. Therefore, cranberries can be useful in the prevention of bacterial adhesion to the urothelial layer[39]. Jepson et al.[40], in a 2008 Cochrane review, showed that cranberry products reduce the incidence of recurrences at 12 months by 39% compared with placebo. On the other hand, these authors, have recently found (2012) no evidence for the use of cranberry prophylaxis. This discrepancy may be justified by widely varying formulations of the product and respective doses[41].

In a randomized clinical trial, Howell et al.[42] demonstrated that intake of a minimum daily dose of 36 mg of proanthocyanidin A is necessary in order to reduce urinary *E. coli* concentration. Kahlmeter et al.[32] compared the effects of TMP-SMX and cranberry prophylaxis on antibiotic resistance among uropathogenic E. coli strains. After only one month of study it was found out that TMP-SMX had higher resistance rates, in comparison to cranberry prophylaxis. This study also showed an increase in resistance to amoxicillin and quinolones during use of TMP-SMX. Beerepoot et al.[43] demonstrated that, in premenopausal women, TMP-SMX (480 mg once daily) is more effective than cranberry capsules (500 mg twice daily) for the prevention of RUTIs. However, this should be weighed against the greater development of antibiotic resistance by TMP-SMX.

An important physiologically protective mechanism against UTI lies in the preservation of the equilibrium of the normal vaginal microbial population due to the presence of different *Lactobacillus* species, as these microorganisms are able to prevent colonization by pathogens. Based on this consideration several studies have investigated if intravaginal *Lactobacillus* administration could

prevent UTI. Stapleton et al.[44] showed that Lactin-V, an intravaginal probiotic composed of *L. crispatus CTV-05*, may reduce the rate of RUTI in women by 50%. Women who had greater colonization with *L. crispatus* had superior protective effects of Lactin-V, which reflects an apparent treatment advantage for Lactin-V over natural recovery of the vaginal microbiota after an episode of RUTI[45].

As discussed earlier, in postmenopausal women, intake of estrogens help to re-establish the normal vaginal flora. Raz et al.[23] demonstrated that vaginal estriol/estradiol-releasing vaginal rings restore vaginal flora, reduce vaginal pH and the number of symptomatic bacteriuria, making it an interesting mechanism to prevent future UTI. However, it appears that oral estrogen does not reduce the incidence of UTI in postmenopausal women, thus intra-vaginal estriol is more effective.

ECE (*Escherichia coli* extract), an immunomodulating preparation containing the lyophilized extract of 18 uropathogens, increases the activity of phagocytes, B-lymphocytes and natural killer cells. Kim KS et al.[45] study demonstrated that ECE was effective and safe for the prophylaxis of recurrent cystitis. Other bacterial preparations have been used to prevent RUTI. Bauer et al.[46] reported a meta-analysis comparing the ability to prevent RUTI of an oral bacterial lysate of *E. coli* and placebo, showing superiority of the lysate. These components activate Toll-like receptors (TLR), leading to enhanced responses of innate immune cells. Furthermore this lysate was well tolerated and patient compliance was excellent in all studies.

In Lorenzo-Gomez et al.[47] study he compared the impact of the prophylactic treatment with a bacterial vaccine (Uromune® which contains an inactivated bacterial cell suspension of selected strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris* and *Enterococcus faecalis*) and the commonly used antibiotic therapy. The group of women that was treated with Uromune®, for a period of 3 months, had an improvement of 75% in the number of UTI when compared with the other group that was under prophylactic antibiotic treatment. The benefit of Uromune® was maintained after an observation period of 9 and 15 months (86 and 77% of improvement, respectively). Oral immunization may induce substantial immune responses in the small intestine (strongest in the proximal segment), ascending colon, and mammary and salivary glands, but it is relatively inefficient at evoking response in the distal segments of the large intestines, tonsils, or female genital tract mucosa. However, sublingual and nasal mucosa can serve as an inductive site for generating a broad spectrum of mucosal and systemic immune responses, including the respiratory and genitourinary tracts with a high degree of efficacy and persistence of the immune response[48]. Considering the clinical impact due to the high prevalence and the high cumulative cost of UTI, together with the increasing resistance to antibiotics, the results obtained in Lorenzo-Gomez et al.[47] study favor the use of bacterial immunostimulation, which could be an effective strategy to reduce frequency, duration, severity, and costs of RUTI in adults and children.

As discussed before, UPEC have FimH adhesins that facilitate the colonization and invasion of these bacteria into uroepithelial cells. Therefore, another promising way to treat and prevent urinary tract infections is by antagonizing these molecules. Cusumano et al.[49] tested the synthesis and therapeutic efficacy of orally active FimH antagonists in mice, and demonstrated their ability to treat chronic UTI and potentiate antibiotic treatment of resistant bacterial infection. These compounds block the FimH-mediated binding of UPEC to uroepithelial cells which prevents formation of IBCs. Cusumano et al. described several compounds and most of them reduced significantly the colonization of the bladder and increased the activity of TMP-SMX (by prolonging exposure to antibiotic levels in the urine), leading to less resistance rates. It was also demonstrated that this approach can be used to prevent IBC formation.

Damiano et al.[50] and Davide de Vita[51] studies provide evidence that intravesical instillation of hyaluronic acid and chondroitin sulphate significantly reduce the incidence of UTI in women with a history of recurrent UTI. They assumed that a damaged glycosaminoglycan layer facilitates bacterial adherence and so, treatment with HA is capable of preventing adherence as it repairs the glycosaminoglycan layer and therefore preventing recurrent UTI. Damiano et al.[50], a placebo-controlled randomized trial, studied 57 women receiving either intravesical instillations of HA-CS or placebo once weekly for 4 weeks, and then once monthly for 5 months. After 12 months it was shown that 48% of these women were recurrence free (a reduction of absolute risk of 77% of RUTI)

Conclusions

Multiple host and bacteria related factors can lead to the development of recurrent UTI. An important step in order to effectively treat these infections is the identification of both predisposing situations and risk factors. Antibiotic therapy is essential to the therapeutic strategy for acute uncomplicated cystitis. However, as discussed earlier, continuous antibiotherapy must be judicious and kept to a minimum thus avoiding adverse effects and increased resistance. Currently, the first-line antibiotics for

treatment of acute uncomplicated UTI are single-dose fosfomycin trometamol (3g), pivmecillinam (400 mg) for three days, or nitrofurantoin macrocrystals (100 mg) twice daily for five days. A possible alternative in the future will be treating only the symptoms of cystitis with ibuprofen, but this hypothesis is still under study.

With regard to antibiotic prophylaxis, continuous, post-coital or self-treatment approach, all have been demonstrated to prevent recurrent uncomplicated UTI. The most commonly used antibiotics for this purpose are Nitrofurantoin, Fosfomycin trometamol, TMP-SMX, cephalosporins or quinolones, all at lower than therapeutic dosages.

In order to avoid antibiotics, cranberries have been used in the prevention of these infections for many years, as they inhibit the bacterial adhesion to the urothelial layer. It has also been shown that intravaginal *Lactobacillus* administration and vaginal application of estriol/estradiol can prevent UTI, by restoring the vaginal flora, reducing vaginal pH and, thereby, symptomatic bacteriuria. Furthermore, *Escherichia coli* extract was proved to be effective and safe for the prophylactic treatment of recurrent cystitis, hence bacterial immunostimulation can be an effective strategy to reduce frequency, duration, severity, and costs of RUTI. Recently, intravesical instillation of hyaluronic acid and chondroitin sulphate was also demonstrated to significantly reduce the incidence of UTI in women with a history of recurrence of those infections. FimH antagonists might also become used has prophylactic weapons. Although more studies are needed, there are already several safe and effective ways to prevent RUTI thereby avoiding antibiotics.

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