REVIEW

An Updated Management of Uncomplicated Recurrent UTI in Women

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Abstract

Management of recurrent UTI is a very topical subject due to the high prevalence of the disease, its influence on the quality of life and the resulting social burden, as well as the increasing ecological adverse effects of the prolonged and repetitive antimicrobial therapy prescribed over the time. Sustained efforts should be made for a better understanding of the risk factors and the pathophysiology of the UTI recurrence, a precise diagnosis and a circumspect attitude regarding the antibiotic prescription. All the alternative therapies must be considered and the best treatment option should be chosen, providing maximum efficiency and minimal risks for the individual and also for the community.

Key words: urinary tract infections, management, antimicrobial therapy.

Introduction

This topic has been discussed very frequently in recent years due to the high prevalence of urinary tract infections (UTI) among women, their significant recurrence rate and, above all, due to the risks of classical therapy for these recurrences. Repetitive and/or prolonged antimicrobial therapy prescriptions produced increases in the rates of antimicrobial resistance, colonization with multidrug-resistance microorganisms ("collateral damage" phenomenon) and contribute to the uprising incidence of Clostridium difficile infection worldwide [1-4].

Definitions and prevalence

According to the recent published American Urological Association (AUA) guidelines, 60 percent of the feminine population experience an acute episode of low UTI (cystitis) in their lifetime [1, 5, 6]. Approximately one third of these patients are prone to another episode and 25-50 % of them may have the misfortune to experience multiple UTI episodes [6-8]. Recurrent UTI (rUTI) are defined as two or

more culture-proved episodes of UTI experienced in a six month period or as three or more UTI episodes within one year; the mandatory condition for the veracity of the definition is that the episodes are separate infections [9]. As for the "culture-proved" term, the newest guidelines admit that a threshold of over 10^5 CFU is needed for asymptomatic patients, but a value of over 10^2 CFU can be enough for patients with a strong clinical suspicion of UTI (characteristic UTI symptoms) [1,10].

Recurrence risk factors

The conditions that predispose to the recurrence of UTI are multiple: anatomical, microbial, behavioral and even genetic. *Anatomic conditions* such as structural urinary tract abnormalities causing obstructions, dysfunctional pelvic support for the bladder and urethra, uterus, vagina, and rectum resulting in any degree of prolapse, genital organs cysts and even a shorter urethral-anal distance can predispose to persistence or reappearance of UTI [11]. *Microbial factors virulence* are considered to be the most important link in the perpetuation of the rUTI. The normal lower urinary tract hosts a microbial community which is very important for the prevention of uropathogens colonization at this level [12]. Disruptions of the normal flora can cause bladder colonization produced by the intracellular progression and survival of the bacterial colonies [13]. This phenomenon appears very quickly after the ascension of the uropathogenic germs in the bladder - in a few hours; type 1 and type P pili are responsible for the persistence of the germs in the urothelium [14-16]. Several *behavioral habits* can influence the prevalence of rUTI. In premenopausal women the most common risk factors for the recurrence of UTI are sexual intercourse, the use of spermicides, diaphragm and/or oral contraceptives. Classic factors enounced to be involved in rUTI development are no longer accepted as certain: bath tub usage, wiping patterns, delayed bladder voiding [13,17]. For postmenopausal individuals the factors often implicated are low estrogen levels, urodynamic disruptions, constipation [13,18].

Some *genetic* polymorphisms are also associated with a higher risk for rUTI due to a decreased cell-mediated bladder defense capacity; toll-like receptors variations, cytokine polymorphisms or deficiencies are the substrate of the familial aggregation of frequent UTI episodes [13,19].

Modern treatment issues in rUTI

While antimicrobial therapy is recognized to be the most efficient method to treat rUTI, the threatening increase of antimicrobial resistance among uropathogens and the uprising incidence of Clostridium difficile infections worldwide has determined a more circumspect attitude regarding the first treatment option in UTI and the development of the antimicrobial stewardship program [1,6,20,21]. However, is very difficult for the physician to adhere to this program and not to prescribe broad-spectrum antibiotics for an extended period of time to a patient presenting with cystitis and a history of excruciating recurrences. However, it is important to know that aggressive treatment of UTI with the intention to eradicate germ colonization can lead to a higher incidence of antibiotic resistance, more frequent upper UTI episodes and to the "collateral damage" phenomenon. [1,6].

Taking into consideration all these issues, recent guidelines strongly recommend to use, as first-line therapy, nitrofurantion, trimethoprim-sulfametoxazol (TMP-SMX) or fosfomycin, chosen according to local resistance pattern. The duration of the treatment should be as short as reasonable, but no longer than seven days, even if we follow the bacterial culture results and we prescribe parenteral antibiotics (*table 1).* Prior to the treatment,

the clinician should perform the urinalysis, culture and sensitivity for each episode, in order to change antibiotic regimen if needed. [6, 22].

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Table 1. *Antimicrobial therapy indicated as first-line options for uncomplicated UTI episodes*

	Nitrofurantoin	**TMP–SMX**	**Fosfomycin**
Efficiency	88–93%	90–100%	83–91%
Spectrum	*E. coli, S. saprophyticus*	*Extended to all typical uropathogens*	*Vancomycin-resistant Enterococci, Extended spectrum beta-lactamase, Gram Negative Rods*
Collateral damage	No	Minimal	No
Administration	100 mg BID x 5days	800/160 mg BID X 3days	3 g single dose

Adapted after American Urological Association guidelines 2019 [6]

Second-line agents are cephalosporins and fluoroquinolones, both having several disadvantages (lack of efficiency, fungal infections, clostridium difficile or extended-spectrum beta-lactamase K pneumonia infections development for beta-lactams; QTc prolongation, aortic aneurism and tendon rupture risks for qiunolones) [1, 23, 24].

A different approach is recommended for asymptomatic rUTI. A positive urine culture in a patient with no symptoms does not require antimicrobial treatment and surveillance, except for the cases programmed for surgical interventions and those with Proteus mirabilis-induced struvite stone formation [6].

Repeated symptomatic UTI episodes defined as rUTI imposes the use of prophylaxis methods. After analyzing several databases, all the guidelines agreed that the most effective way to eradicate/lower the UTI episodes is the prolonged antimicrobial treatment [6, 21, 22]. There are moderate-to-strong recommendations for a low dose of antimicrobial agent prescribed in a single evening dose or three doses per week or even as an after-intercourse dose. The agents of choice are listed in table 2 and the duration of the treatment can vary between 3 - 12 months [25 - 31]. For women with frequent UTI episodes related to sexual activity the guidelines recommendations are for one single pre or post-coital antibiotic dose [6, 21, 22].

Table 2. *Antimicrobial prophylaxis in rUTI*

Antimicrobial agent	***Dose***	***Possible adverse effects***
Nitrofurantoin monohydrate macrocristals	50 - 100 mg/day	Pulmonary toxicity, hepatotoxicity, peripheral neuropathy; avoid in eldery and in CKD $\geq$ stage 4
TMP-SMX	40/200 mg daily or thrice weekly	Skin eruptions including Stevens-Johnson syndrome, gastrointestinal and hematologic disturbances
Cephalexin	125-250 mg daily	Fungal infection, increased INR
Fosfomycin	3 g every 10 days	Gastrointestinal disorders, vaginitis

Adapted after American Urological Association guideline 2019 [6]

The efficacy of antimicrobial prophylaxis is counterbalanced by many inconveniences. First of all, based on many years of RCT studies, the guidelines agreed that, after the antibiotic administration period, the prevalence of rUTI episodes returns to the pre-treatment level. [6, 21, 22]. Second, antibiotic resistance may develop and the possibility of selecting multidrug-resistant strains is considerable [32, 33]. Specific adverse effects of each antibiotic drug and the risk of intestinal flora disturbance are also important problems to take into consideration after long-term antimicrobial prophylaxis.

For all the reasons mentioned above, there is an increasing interest in replacing the antibiotic prophylaxis in rUTI with other alternatives. Scottish guidelines recommend cranberry products as the first-line option in the non-antimicrobial treatment for rUTI. Based on the properties of proanthocyanidins (PACs) to block type P pili of E Coli and K pneumonia, with beneficial reduced bacterial adhesion to the urothelium, cranberry products are able to reduce the recurrences after a first acute UTI episode [34, 35]. The use of standardized tablet formulation in high strength doses is advised and the lack of adverse effects is an important argument for this treatment. It also seems that the association of PAC to TMP-SMX treatment can reduce the resistance development in patients treated with a combination of the two [36].

United States guidelines for UTI advises the use of D-mannose for blocking the uropathogens adherence to the urothelium trough the action of type 1 pili, in a 2 grams per day dose, prescribed for 3 - 6 months and without any adverse effects [22].

Methenamine hippurate is an urinary antiseptic used in the 80's, experiencing a return of interest in the recent years; many studies in progress show encouraging results, especially in catheterized patients [37]. Another antiseptic alternative for catheter-associated UTIs is represented by methylene blue potentiated by potassium iodide [38].

Immunoactive therapy is a customary option to be tried, with oral OM-89 or injectable annihilated strains of uropathogen E Coli (UPEC) as the most important representatives, but effective just as longer as the treatment is ongoing [39, 40]. Scandinavian practitioners prescribe acupuncture, effective by improving micturition dynamics, in 4 weeks-long sessions, with a notably improvement of the UTI episodes prevalence [41 - 45].

Local therapies are also proposed for improving the quality of life and lowering the recurrences of UTI. While estrogens or lactobacillus used via intra-vaginal route are already accepted used options with arguable results, the newer method of intravesical hyaluronic acid once a week for 4 weeks consecutively plus chondroitin injections is much more promising [6, 46 - 48].

Conclusions

Although it is a pathology known from ancient times, UTI management still necessitates concerted efforts and sustained interest of medical researchers. Because of the rUTI increased prevalence and its effects on the quality of life, and due to the ecological adverse effects of the antimicrobial therapy utilized for its cure, it is necessary to develop new therapeutic strategies with increased efficiency and minimal risks.

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Received: January 15, 2020

Accepted: February28, 2020