

Recurrent Urinary Tract Infections Management in Women

A review

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الالتهابات المتكررة للمسالك البولية عند النساء وطرق علاجها

مراجعة

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الملخص: التهابات المسالك البولية (عدوى المسالك البولية) هي واحدة من الالتهابات البكتيرية السريرية الأكثر شيوعاً لدى النساء، وهو ما يمثل ما يقرب 25% من جميع حالات العدوى. وحوالي 50-60% من النساء يصابن بعدوى المسالك البولية في حياتهن. بكتيريا *Escherichia coli* هي أكثر كائنات مسبب عدوى المسالك البولية في معظم المرضى. العدوى مرة أخرى هي السبب الأساسي في الإصابة بعدوى المسالك البولية المتكررة من قبل نفس المريض. الجماع المتكرر هو واحد من أعظم عوامل الخطر لعدوى المسالك البولية المتكررة. في مجموعة الأفراد المصابين بظروف مرضية إضافية، يمكن لعدوى المسالك البولية المتكررة أن تؤدي إلى التهابات المسالك العلوية أو انتان بولي. على الرغم من أن العلاج الأولي هو العلاج المضاد للميكروبات، استخدام نظم وقائية مختلفة واستراتيجيات بديلة، هي طرق متاحة للحد من التعرض للمضادات الحيوية.

مفتاح الكلمات: عدوى المسالك البولية؛ العلاج؛ الوقاية باستخدام المضادات الحيوية؛ الوقاية.

ABSTRACT: Urinary tract infections (UTIs) are one of the most frequent clinical bacterial infections in women, accounting for nearly 25% of all infections. Around 50–60% of women will develop UTIs in their lifetimes. *Escherichia coli* is the organism that causes UTIs in most patients. Recurrent UTIs (RUTI) are mainly caused by reinfection by the same pathogen. Having frequent sexual intercourse is one of the greatest risk factors for RUTIs. In a subgroup of individuals with coexisting morbid conditions, complicated RUTIs can lead to upper tract infections or urosepsis. Although the initial treatment is antimicrobial therapy, use of different prophylactic regimens and alternative strategies are available to reduce exposure to antibiotics.

Keywords: Urinary Tract Infection, therapy; Antibiotic Prophylaxis; Prevention.

URINARY TRACT INFECTIONS (UTIs) occur more often in women than in men, at a ratio of 8:1. Approximately 50–60% of women report at least one UTI in their lifetime, and one in three will have at least one symptomatic UTI necessitating antibiotic treatment by age 24.¹⁻³

Normally, the urinary tract is sterile, but bacteria may rise from the perianal region, possibly leading to UTI. Pathogens in the bladder may stay silent or can cause irritative symptoms like urinary frequency and urgency, and 8% of women may have asymptomatic bacteriuria. If bacteria enter the blood stream, they could cause severe complications, including septicaemia, shock and, rarely, death.^{4,5} The definition of recurrent urinary tract infection (RUTI) is three UTIs with three

positive urine cultures during a 12-month period, or two infections during the previous 6 months.⁵⁻⁸

This article provides an up-to-date review of the epidemiology, pathophysiology, risk factors, diagnosis, management and prevention of RUTIs in women.

Classification of Urinary Tract Infections

UTIs are classified into 6 categories. The first category is an *uncomplicated infection*; this is when the urinary tract is normal, both structurally and physiologically, and there is no associated disorder that impairs the host defense mechanisms. The second category is an *complicated infection*; this is

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when infection occurs within an abnormal urinary tract, such as when there is ureteric obstruction, renal calculi, or vesicoureteric reflux. The third category, an *isolated infection*, is when it is the first episode of UTI, or the episodes are 6 months apart. Isolated infections affect 25–40% of young females. The fourth category, an *unresolved infection*, is when therapy fails because of bacterial resistance or due to infection by two different bacteria with equally limited susceptibilities. The fifth category, *reinfection*, occurs where there has been no growth after a treated infection, but then the same organism regrows two weeks after therapy, or when a different microorganism grows during any period of time.^{9,10} This accounts for 95% of RUTIs in women. Bacterial persistence happens when therapy is impaired by the accumulation of bacteria in a location that cannot be reached by antibiotics, such as infected stones, urethral diverticula and infected paraurethral glands. The sixth category, *relapse*, is when the same microorganism causes a UTI within two weeks of therapy; however, it is usually difficult to distinguish a reinfection from a relapse.¹¹

Epidemiology and Pathophysiology

UTIs are one of the most frequent clinical bacterial infections in women, accounting for nearly 25% of all infections. Around 50–60% of women will experience a UTI in their lifetime.^{2,9} The estimated number of UTIs per person per year is 0.5 in young females.¹² Recurrences usually occur within three months of the original infection, and 80% of RUTIs are reinfections.¹³ The incidence of UTI increases with age and sexual activity.¹⁴ Post-menopausal women have higher rates of UTIs because of pelvic prolapse, lack of oestrogen, loss of *Lactobacilli* in the vaginal flora, increased periurethral colonisation by *Escherichia coli* (*E. coli*), and a higher incidence of medical illnesses such as diabetes mellitus (DM).¹⁵ The microorganism that causes RUTIs is similar, in most cases, to the sporadic infection. Most uropathogens from the rectal *flora* ascend to the bladder after colonising the periurethral area and urethra.

Despite the fact that most *E. coli* are eradicated by the host defence mechanisms within days, only small clusters of intracellular *E. coli* are observed

to persist for several months in an antibiotic-resistant state.¹⁶ Reactivation of uropathogenic *E. coli* (UPEC), an intracellular bacteria, could cause RUTIs.¹⁷

Other significant pathogens that can cause UTI include *Proteus mirabilis*, *Staphylococcus saprophyticus*, *Staphylococcus epidermidis*, and *Klebsiella pneumoniae*.¹⁸ In diabetic patients, *Klebsiella* and group B *streptococcus* infections are more common. *Pseudomonas* infections are more common in chronically-catheterised patients.^{18,19}

Risk factors for RUTI in sexually-active premenopausal women are the onset of symptoms shortly after sexual intercourse, the use of spermicides for contraception, taking on new sexual partners, the age of the first UTI, a maternal history of UTI and voiding dysfunction.^{5,8,20,21} Many other factors have been thought to predispose women to RUTIs, such as voiding patterns pre- and post-coitus, wiping technique, wearing tight undergarments, deferred voiding habits and vaginal douching; nevertheless, there has been no proven association.²² Medical conditions such as pregnancy, DM and immunosuppression increase a woman's risk of RUTI by facilitating the access of uropathogens overcoming normal host defense mechanisms.²³ Patients with DM have a higher risk of asymptomatic bacteriuria, RUTIs and pyelonephritis.²⁴

Clinical Presentation and Diagnosis

Common symptoms of a UTI are dysuria, urinary frequency, urgency, suprapubic pain and possible haematuria. Systemic symptoms are usually slight or absent. The urine may have an unpleasant odour and appear cloudy.²³ Diagnosis of RUTI depends on the characteristic of clinical features, past history, three positive urinary cultures within the previous 12-month period in symptomatic patients and the presence of neutrophils in the urine (pyuria).^{7,8,21} Irritative voiding symptoms are present in 25–30% of women with RUTIs.²⁵ The probability of finding a positive culture in the presence of the above symptoms and the absence of vaginal discharge is around 81%.²⁶ In a complicated UTI, such as pyelonephritis, the symptoms of a lower UTI will persist for more than a week with systemic symptoms of persistent fever, chills, nausea and

vomiting.²⁵

A recent study showed how to distinguish the clinical symptoms of a RUTI from irritative voiding symptoms (urgency, dysuria and frequency) without infection. Women with RUTIs were more likely to experience symptoms after intercourse, have a previous history of pyelonephritis, and experience rapid resolution of symptoms post-antibiotic therapy than those women with irritative voiding symptoms.^{5,6} Moreover, women with RUTIs were more unlikely to report nocturia and have symptoms between episodes of UTI than women without infection. The presence of irritative voiding symptoms between perceived episodes of UTI suggests a non-infectious cause as seen in interstitial cystitis, urethral syndrome or detrusor muscle overactivity.^{5,27}

Women with RUTIs should have an initial evaluation including a history-taking and a physical and pelvic examination; the latter is important to detect pelvic organ prolapse and to assess the status of the vaginal epithelium.²⁸ Urinalysis and urine culture with sensitivity are also valuable investigations. Women with a positive family history of DM, obesity or RUTI must be screened for DM.^{28,29} Women with suspected urine retention need to be evaluated for high post-void residual urine volume.

Urine culture and sensitivity testing are the standard diagnostic investigations to detect the causative organism and to determine the type of antimicrobial therapy needed.^{8,21} A UTI is defined as a positive urine culture with greater than 100,000 colony-forming units (cfu)/ml. In acute cystitis, even 1,000 cfu/ml and in acute pyelonephritis 10,000 cfu/ml may be sufficient for diagnosis in a symptomatic patient. A urine culture is recommended in a RUTI or in the presence of complicating factors.^{9,21} A urine culture can remain positive for more than two weeks even after treatment in cases of chronic UTIs or RUTIs. A 'clean-catch' or midstream technique needs to be used when collecting the urine sample, which reduces the risk of vaginal and skin contamination to approximately 30%.³⁰ Urinalysis, either by dipstick or microscopy, for the detection of pyuria, as a method for predicting a UTI has a sensitivity of 80–90% and a specificity of 50%, but it only detects those bacteria which reduce nitrates to nitrites in the urine. Bacteria such as *Staphylococcus*

saprophyticus lack that enzyme, which makes the nitrite test considerably less useful. Dipstick analysis for leukocyte esterase (the enzyme produced by neutrophils) is indirect and is the least expensive test that detects pyuria with a sensitivity of 72–97% and a specificity of 41–86%, as organisms other than uropathogens can also produce leukocyte esterase.³¹

More advanced investigations, such as cystoscopy, are advised in women over the age of 50.³² Ultrasound of the kidneys, an intravenous pyelogram (IVP) and a computed tomography (CT) scan can help in detecting congenital structural urogenital anomalies.⁹

Management of Recurrent Urinary Tract Infections (RUTIs)

COUNSELLING

Women with RUTIs should be educated about the characteristics of reinfection and relapse; the proper way to practice post-coital voiding; the importance of avoiding skin allergens, tight clothing and bubble baths; ways to ensure personal hygiene, and the choice of alternative forms of contraception rather than spermicides.^{21,33,34}

GENERAL THERAPIES

Patients should be advised and encouraged to drink plenty of fluids (two to three litres per day) and to urinate frequently to help flush bacteria from the bladder. Holding urine for a long time allows bacteria to multiply within the urinary tract, resulting in cystitis. Preventive measures related to sexual intercourse may reduce the recurrence rate. Moreover, women are encouraged to clean the genital areas before and after sex and to wipe from front to back, which will reduce the spread of *E. coli* from the perigenital area to the urethra.³⁵ Avoiding multiple sexual partners will reduce the risk of both UTIs and sexually transmitted infections. Women are encouraged to avoid spermicidal contraceptives, diaphragms and vaginal douching, which may irritate the vagina and urethra and facilitate the entry and colonisation of bacteria within the urinary tract. Skin allergens introduced to the genital area, such as bubble bath liquids, bath oils, vaginal creams and lotions, deodorant sprays or soaps are better avoided as they could alter vaginal *flora* and

ultimately result in UTIs.³⁶

ANTIMICROBIAL THERAPY

Antimicrobial therapy is the core treatment for UTIs, with the main objective being the eradication of bacteria growth in the urinary tract through an efficacious, safe and cost-effective antimicrobial agent. This can be achieved within hours if the antibiotics are maintained at sufficient urine levels.³⁷ In order to ensure compliance and be patient-friendly, the drug should be given for a short period of time to prevent bacterial resistance. Antimicrobial agents should be prescribed according to the susceptibility of the infecting bacteria, the concentrations of uropathogens in the urine and the urinary complaint. This is important to consider when there is septicaemia or parenchymal infection, as antimicrobials are usually at higher levels in the urine than in serum.³³

Dose modification is required for patients with renal insufficiency and in the case of other factors such as: age, pregnancy or lactation status, primary or recurrent infections, hospitalised patients, DM, liver disease, an immunocompromised state, hydration levels and psychiatric problems.³⁴

A variety of antimicrobials are used for the prevention and management of RUTIs.^{6,15,24,29,33,38–41} A Cochrane review has shown that antibiotics in comparison to a placebo are more effective in preventing recurrences in pre- and post-menopausal women with RUTIs.⁶ The criteria for the selection of the most effective antibiotic depend on a patient's pattern of resistance, adverse effects, interaction with drugs and cost.

Ampicillin, amoxicillin, and sulfonamides are no longer the drugs of choice for empirical treatment because of the widespread emergence of resistance in 15–20% of *E. coli* in several areas of the USA and other countries.^{18,42–44} Nitrofurantoin or amoxicillin/clavulanic acid remain effective in terms of bacterial sensitivity, but nitrofurantoin needs to be avoided in patients with pyelonephritis because of its poor serum and tissue levels. Less than 5% of *E. coli* strains are resistant to nitrofurantoin, whereas other strains are often resistant to it. The rate of *E. coli* resistance to fluoroquinolones, even in uncomplicated UTIs, varies between countries with rates reported as 0.5–7.6% in Europe,⁴⁵ 15% in Korea,⁴⁶ and up to 35% in some parts of India.⁴⁷

Penicillins and cephalosporins are considered safe during pregnancy, but trimethoprim, sulphonamides, and fluoroquinolones should be avoided. Oral antibiotic therapy resolves 94% of uncomplicated UTIs, although recurrence is not uncommon. In the recently published *International Clinical Practice Guidelines for the Treatment of Acute Cystitis*, a 3-day regimen of trimethoprim-sulfamethoxazole (TMP-SMX) and a 5-day course of nitrofurantoin are recommended as a first-line therapy for the management of uncomplicated UTIs. A 5-day course of nitrofurantoin has an efficacy equivalent to a 3-day TMP-SMX course.^{48,49} A 3- to 7-day regimen of beta-lactams, such as cefaclor or amoxicillin/clavulanic acid, is appropriate when first-line therapies cannot be used.^{43,48} Although a 3-day course of fluoroquinolones can be quite effective, it is not usually recommended as first-line therapy because of the emerging resistance to them and their potential side effects, as well as the high cost; nevertheless, fluoroquinolones are the drug of choice in women who are experiencing low tolerance or an allergic reaction after empirical therapy.^{48,50} In a meta-analysis, a single-dose regimen of fosfomycin trometamol has been shown to be a safe and effective alternative for the treatment of UTIs in both pregnant and non-pregnant women, as well as in elderly and paediatric patients, but it seems to be slightly less effective than the above mentioned therapies.^{43,48,51} Pivmecillinam in a 3- to 7-day course is also effective, but not available in most regions. Because of its poor efficacy, amoxicillin and ampicillin should not be used for the empirical treatment of UTIs.⁴⁸

TMP-SMX and fluoroquinolones prevent RUTI by inhibiting the recovery rate of uropathogens (especially *E. coli*) from the faecal reservoir,⁵² while nitrofurantoin plays its role in the treatment of RUTI by sterilising the urine and inhibiting bacterial attachment.^{24,53,54} A follow-up urinalysis and urine culture, also called the 'test of cure', is not indicated in women with uncomplicated UTIs, but should be performed in those women who are suffering from RUTIs or a complicated UTI.

Different antibiotic prophylaxis regimens such as continuous prophylaxis, post-coital prophylaxis and acute self-treatment are important management strategies in preventing RUTIs. Patient self-treatment is recommended in cases of those with ≤ 2 episodes of UTIs per year, whereas continuous

antimicrobial prophylaxis, low-dose prophylaxis, or post-coital prophylaxis is generally considered in ≥ 3 episodes of UTIs annually.²⁴

CONTINUOUS ANTIBIOTIC PROPHYLAXIS

Continuous prophylaxis is considered when simple measures fail. For this purpose, low-dose antibiotics can be given daily for 6 months or longer. Some physicians advise prophylaxis on alternate nights or 3 nights per week. One study showed that prophylaxis given weekly was more effective than one given monthly, but there is no study comparing daily and weekly regimens.^{6,21,55}

POST-COITAL ANTIBIOTIC PROPHYLAXIS

When a RUTI is related to sexual activity, post-coital therapy is considered an effective alternative prophylactic approach.^{21,28,56} Post-intercourse prophylaxis has fewer side effects than daily prophylaxis, as antibiotic consumption is reduced to only one-third.⁵³ After intercourse, a single dose of the most common antibiotics is used, such as nitrofurantoin, TMP-SMX or a fluoroquinolone.^{21,54} Studies have shown that women using continuous or post-coital prophylaxis will report about 1.2 to 1.3 UTIs per year within 6 months of stopping the treatment.⁶

ACUTE SELF-TREATMENT

The patient self-treatment management strategy is an ideal effort to decrease overall antibiotic consumption, and for women who are not suitable candidates for long-term daily prophylaxis. Schaeffer showed that “self-start therapy” should be confined to those women who are self-motivated and have good compliance.⁵⁷ A patient needs to consult a physician immediately if she becomes pregnant or if there is any change in symptoms, an increased recurrence of episodes of infection, or no change in symptoms within 48 hours of antimicrobial treatment. These patients can effectively self-treat RUTIs by initiating a standard 3 day course of recommended antimicrobials with minimum side effects.⁵⁸

Adjuvant Measures

OESTROGEN

Oestrogen use stimulates the proliferation of *Lactobacillus* in the vaginal epithelium, reduces pH and avoids vaginal colonisation by uropathogens. After the menopause, oestrogen levels and *Lactobacilli* numbers drop; this plays a significant role in the development of bacteriuria, and makes post-menopausal women susceptible to UTIs. Vaginal oestrogen use reduces RUTIs by 36–75% and has minimal systemic absorption. Based on a Cochrane review in post-menopausal women with RUTIs, when compared to a placebo, vaginal oestrogens were found to prevent RUTIs, but oral oestrogen did not have the same effect.^{59,60} Local oestrogen cream twice a week and an oestradiol-releasing vaginal ring are both effective in reducing RUTI attacks.^{59,61,62} They restore vaginal flora, reduce pH and therefore reduce UTIs; however, the reappearance of vaginal *Lactobacilli* takes at least 12 weeks when using an oestrogen vaginal ring.^{61–63} Although evidence does not support using a particular type or form of vaginal oestrogen topical creams are cheaper than an oestradiol-releasing vaginal ring but have more side effects.^{21,57,59,64}

CRANBERRY JUICE AND TABLETS

Cranberry juice and tablets have been shown to reduce RUTIs as they contain a compound called tannin, or proanthocyanidin, which reduces *E. coli* vaginal colonisation.^{65,66} Although earlier, smaller studies have shown that consuming cranberry juice or tablets can prevent RUTIs, an updated Cochrane review showed that evidence for its benefit in preventing UTIs is small; therefore, cranberry juice cannot be recommended any longer for UTI prevention.^{21,67–69}

ACUPUNCTURE

Recent studies indicate that the rate of cystitis among cystitis-prone women treated with acupuncture was one-third the rate of that among untreated women and half the rate among women treated by sham acupuncture. Therefore, acupuncture may prevent RUTIs in healthy adult women.^{21,70,71}

PROBIOTICS

Probiotics are beneficial microorganisms that could protect against UTIs. *Lactobacilli* strains are the

best-known probiotics and are found in fermented milk products, mainly yogurt. Other probiotics include *Lactobacilli bifidobacteria*, *rhamnosus*, *casei*, *planetarium*, *bulgaricus* and *salivarius*; *Streptococcus thermophiles* and *Enterococcus faecium*. Reid *et al.* showed *in vitro* that *lactobacillus* can prevent uropathogen infections.^{72,73} Other trials have showed that *L. rhamnosus gr-1* and *L. fermentum rc-14* can colonise the vagina, which could subsequently prevent UTIs. Nevertheless, more clinical studies need be carried out to determine their role in RUTI prevention.^{72–76}

IMMUNOPROPHYLAXIS

Immunoprophylaxis taken orally may prove an effective alternative to antibiotics in the prevention of RUTIs. A meta-analysis of 5 studies showed that oral immunoprophylaxis with the Uro-Vaxom® *E. coli* extract (Terra-Laba, Zagreb, Croatia) taken for a period of 3 months was effective in preventing RUTIs over a period of 6 months.⁷⁷ Another double-blind study has confirmed that *E. coli* extracts are efficient and well-tolerated in the treatment of UTIs, reducing the need for antibiotics and preventing RUTIs.⁷⁸

Other Therapies

Methenamine hippurate is used for prophylaxis and treatment of RUTIs. Methenamine is hydrolysed to ammonia and formaldehyde when in acidic urine, which act as a bactericide to some strains of bacteria.⁷⁹ They are well-tolerated and have mild adverse effects, such as gastrointestinal upsets, rashes, anorexia, and stomatitis. Patients should be informed regarding adequate hydration, adverse effects and the need to avoid milk products and antacids to help keep the urine acidic. A recent Cochrane review on the use of methenamine hippurate concluded that short-term use is effective in preventing RUTIs in patients with a normal renal tract. Nevertheless, it is not effective in women who have urinary tract abnormalities or a neuropathic bladder.^{80,81}

Recurrent Urinary Tract Infection in Pregnancy

UTI is the most frequent medical complication of pregnancy. The risk factors of preterm delivery,

low infant birth weight and abortions are most commonly associated with symptomatic and asymptomatic bacteriuria during pregnancy.⁷⁷ In pregnancy, factors that contribute to UTI risk are ureteric and renal pelvis dilation; increased urinary pH; decreased muscle tone of the ureters, and glycosuria, which promotes bacterial growth. Treatment of asymptomatic bacteriuria in pregnancy reduces the risk of pyelonephritis. As RUTIs are common in pregnancy, they need prophylactic treatment if they occur. Screening for bacteriuria is recommended in all pregnant women at their first prenatal visit and then in the third trimester.^{82,83} They should subsequently be treated with antibiotics such as nitrofurantoin, sulfisoxazole or cephalexin.^{21,24,82–84} Antibiotic prophylaxis for RUTI in pregnant women is effective using continuous or post-coital regimens. The causative organisms of UTI in pregnancy are similar to those found in non-pregnant patients, with *E. coli* accounting for 80–90% of infections.^{85,86} Urinary group B streptococcal infections in pregnant women need to be treated and followed by intrapartum prophylaxis.²¹

Conclusion

UTIs are some of the most frequent clinical bacterial infections in women. RUTIs are less common and are mainly caused by reinfection by the same pathogen. Women with RUTIs need to be properly investigated by urinalysis, urine cultures and other radiological techniques in order to rule out causes of recurrence, as well as to assess possible anatomical or functional urinary tract abnormalities. Although standard UTI therapy starts with antimicrobial therapy, alternative strategies are available to reduce exposure to antibiotics, such as the use of methenamine salts, probiotics, cranberry juice, immunoprophylaxis and vaginal oestrogens in post-menopausal women. Continuous antibiotic prophylaxis, postcoital prophylaxis, and acute self-treatment are cost-effective treatment strategies for reducing the number of RUTIs in some patients.

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