**Game-Changing Antibiotic Solutions for Chronic UTIs in Women**

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**Abstract**

Urinary tract infections (UTIs) are prevalent in primary healthcare settings, with persistent recurrences posing significant challenges. These recurrences necessitate extended antibiotic use, adversely affecting patients' quality of life, mental health, and physical activity. The evolving defense mechanisms of bacteria against the host immune system and antibiotics complicate treatment. This article examines the pathomechanisms of recurrent UTIs, focusing on bacterial defense factors. Understanding these mechanisms is essential for developing innovative treatments, particularly non-antibiotic methods, to reduce antibiotic use and its associated side effects, thereby improving patients' overall well-being. The review synthesizes current knowledge on the pathomechanisms, diagnostics, and treatments for recurrent UTIs, emphasizing the impact on patients' mental and physical health. It highlights innovative, non-antibiotic treatment approaches.

**Objectives:** Review and presentation of the current state of knowledge about pathomechanisms, diagnostics and treatment methods used in recurrent urinary tract infections, taking into account the impact on the patient's mental and physical condition. Review of innovative, non-antibiotic methods of treating UTI.

**Material and methods:** Analysis of the studies available on open access sources at PubMed, Google Scholar, National Library of Medicine and Coachrane*.* The research was conducted through word analysis key words such as: „urinary tract infections”, "recurrent infections”, „cystitis”, „bacterial resistance”, „antibiotics”. Selection criteria for articles included consideration of their title, abstract, and publication date, with a focus on English-language publications.

**Results:**

Results of data analysis illustrate the complexity of recurrent UTIs, highlighting the intricate bacteria-host interactions and multifaceted pathomechanisms. Chronic antibiotic therapy and recurrent infections are shown to negatively affect mental and physical health. The discussion covers antibiotic and non-antibiotic treatment methods, advocating for non-antibiotic strategies as the future primary approach for managing recurrent UTIs.

**Keywords :** urinary tract infections; recurrent UTI; UTI management; UTI in women; cystitis;

**Abbreviations**: UTI – Urinary Tract Infections, rUTI – recurrent Urinary Tract Infections, EAU -Association of Urology, AUA American Urological Association, CUA - Canadian Urological Association, SUFU - Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction, PLUS - Prevention of Lower Urinary Tract Symptoms

1. **Introduction**

Urinary tract infections are one of the most frequent conditions in primary health care. It is estimated that up to 50-70% of women have experienced UTI at least once in their lives. 10-30% women without risk factors of complicated UTI develop recurrent Urinary Tract Infection (rUTI). Frequent recurrences pose a serious liability for patients, require long-term use of antibiotics and reduce quality of life[[1]](#endnote-1).

By definition, rUTI is ≥2 acute UTIs in a span of 6 months or ≥3 cases in a year. Clinically it mostly runs as reinfection (recurrence) - cystitis symptoms return 2 weeks after the end of treatment and are usually caused by another bacteria[[2]](#endnote-2). Recurrence should not be confused with relapsing infection which appears 2 weeks before antibiotherapy completion and is induced by the same microbe. It is crucial to distinguish these types from each other, because recurrences may indicate the presence of a bacterial source like kidney stone or abscess. Women are much more susceptible to infection than men, which is due to anatomical reasons such as short urethra, proximity to the anus, vaginal vestibule as a reservoir of microorganisms. Despite the physiological predisposition to UTI in women, it is worth knowing the difference between complicated and uncomplicated UTI. Complicated Infection occurs when it is caused by an atypical pathogen, local or systemic defense mechanisms are impaired, the woman's urine outflow is compromised or involves pregnant women. This classification is important in the selection and duration of treatment. However even immunocompetent patients may have recurrent infections related to decreased host defense[[3]](#endnote-3).

**2. State of knowledge**

**2.1 Pathomechanisms**

There are two main pathomechanisms of rUTI. First is abnormal host defense mechanisms like dysfunctional urothelial barrier, malfunction in bacterial detection and anatomical disorders. Second is bacterial qualities, such as production of proteins enabling survival in the urinary bladder after antibiotic therapy and the ability to create intracellular forms[[4]](#endnote-4).

**2.1.1 Host factors**

An increased incidence of UTI has been observed among female first-degree relatives. This prompted scientists to investigate the connection between genetic factors and local immunity. Cells with Toll-like receptors (TLR) are important elements of innate immunity in the urinary tract. TLRs activate the immune response by recognizing Pathogen-Associated Molecular Patterns (PAMPs) like bacterial lipopolysaccharide (LPS), flagellin and lipopeptides. TLR receptor polymorphisms were genotyped in a cross-sectional analysis[[5]](#endnote-5), [[6]](#endnote-6)**.** TLR5 C1174T the flagellin-binding variant was found to increase rUTI risk. TLR2 G2258A variant, which inhibits lipopeptide signaling, has been associated with an increased risk of asymptomatic bacteriuria. On the other hand, TLR1 G1805T and TLR4 A896G variants are highly likely to prevent rUTI. Due to this study, we can relate the TLR polymorphism with impaired pathogen identification, which in turn is associated with more frequent UTI.

Among women, there are two age groups with an increased incidence of rUTI. During menopause, the amount of estrogen decreases, which affects the vaginal epithelium[[7]](#endnote-7). Epithelial cells produce less and less glycogen, which is a substrate for Lactobacillus species to produce lactic acid[[8]](#endnote-8).As a result, the vaginal pH increases and changes appear in the local microflora. Dysbiome promotes the adhesion of pathogens to the epithelium and, consequently, the occurrence of infections. Research shows that the urinary microbiome may be related to the patch mechanism of rUTI in this group of patients, which may become the target of therapy in the future. The second risk group consists of young sexually active women without predisposing factors, such as anatomical or functional abnormalities[[9]](#endnote-9). Pending intercourse, the microbiome is transferred from the vagina to the urinary tract. Also spermicide usage, sexual partners rotation, delaying micturition after intimacy conduce to UTI.

Another contributing factor are anatomical defects, like bladder or Urethral diverticula, fistulous, leading to functional disorders. As estrogen levels decline, there are reproductive tissue modifications. Pelvic floor muscles are depressed, which may contribute to urinary incontinence or overactive bladder. To rule out an incomplete defecation, post-void residual volume should be taken into account in the diagnostics[[10]](#endnote-10). Various conditions predispose to such functional disorders, including spinal cord paralysis, diabetes and hypothyroidism. Interestingly, up to 1/3 of women with chronic LUTS suffer from hypothyroidism[[11]](#endnote-11). When this group of patients develops an infection, the symptoms of thyroid hormone deficiency become more severe, and in extreme cases Myxedema coma occurs[[12]](#endnote-12).

**2.1.2 Bacterial factors**

Even 75% rUTI cases are caused by uropathogenic Escherichia coli (UPEC). Other frequently found microbes include Enterococcus faecalis, Proteus mirabilis, Klebsiella, or Staphylococcus[[13]](#endnote-13). Bacteria have developed special structures and metabolic pathways that facilitate the invasion of host tissues and also protect against its immune mechanisms. Most often, these bacteria are transferred from the intestine to the urethra, and from there they migrate to the bladder and upper urinary tract. Bacteria are well adapted to these activities thanks to structures such as fimbriae, pili and flagella. The first and most crucial stage of invasion is the bacterial adhesion to uroepithelium[[14]](#endnote-14). This stage is possible due to pili, which have affinity for uroplakins, integrins and other uroepithelial receptors. Interactions between host cell receptors and bacterial adhesins trigger metabolic pathways that enable bacteria to form intracellular bacterial communities (IBCs). IBCs replicate in the cells of the outer layers of the uroepithelium and then invade neighboring cells. In turn, in deeper transitional cells, UPEC can form Quiescent intracellular reservoirs (QIR) - a set of 4-10 metabolically inactive forms separated by a membrane. QIR allows bacteria to survive in the urinary tract for many months to become activated at the right moment and initiate an infection. This is a very key mechanism that may explain the ineffectiveness of antibiotic therapy[[15]](#endnote-15)**.** An equally important feature of bacteria is the ability to create a biofilm from polysaccharides, exogenous DNA, glycoproteins, nutrients and signaling compounds[[16]](#endnote-16). This formation has a high viscosity, which hinders the effective response of the host's immune system and constitutes a barrier to antibacterial drugs. Moreover, bacteria secrete enzymes that break down host structures. They destroy the uroepithelium, which causes symptoms typical of UTI. It is worth emphasizing the role of hemolysin, which has affinity for the host cell membrane[[17]](#endnote-17). At the same time, they obtain nutrients necessary for the growth of bacteria. Bladder cells are low in iron, and this element is essential for functioning, so bacteria have evolved a siderophore system that allows them to take up iron[[18]](#endnote-18).

**2.2. Diagnosis**

The primary symptoms of UTI in the course of cystitis are dysuria, frequent urination, nocturia, and pain in the lower abdomen. If the upper urinary tract is affected, general symptoms appear such as fever, nausea, pain in the lumbar region, and positive Goldflam’s sign[[19]](#endnote-19).

The basic diagnostic tests, in the case of UTIs are urinalysis and urine culture with an antibiogram. The amount of bacteria present in urine is considered diagnostically significant, depending on the method of urine collection2:

 ≥ 103 uropathogens/mL in midstream urine in acute uncomplicated cystitis in women.

 ≥ 104 uropathogens/mL in midstream urine in acute uncomplicated pyelonephritis in women.
 ≥ 105 uropathogens/mL in midstream urine in women or 104 uropathogens/mL in straight catheter urine in women with complicated UTI.

 In a suprapubic bladder puncture specimen, any count of bacteria is relevant.

Diagnostics using a dipstick test are characterized by low effectiveness, therefore traditional diagnostic methods are preferred in rUTI[[20]](#endnote-20). Moreover, urine culture may be useful in distinguishing between recurrence and relapse.

The history of cultures collected in medical records allows to assess the effectiveness of treatment, develop strategies and select antibiotics depending on the sensitivity of the bacteria. If there is no correlation between symptoms and the collected documentation, another cause or coexistence of another disease should be considered.

There is some variation in the guidelines for the management of rUTI developed by European Association of Urology (EAU) (2022) and the combined American Urological Association (AUA) /Canadian Urological Association(CUA)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) (2019)[[21]](#endnote-21). According to AUA/CUA/SUFU, each acute episode requires a urine culture. EAU, on the other hand, in case of typical symptoms and effective antibiotic therapy, there is no need to perform culture. However, both societies present the same position regarding the performance of additional tests and believe that they should not be performed routinely due to their low diagnostic value. Cystoscopy is an important test when hematuria occurs. It allows to exclude bladder cancer[[22]](#endnote-22). Cystoscopy is also useful in the case of bladder stones, recurrent microscopic hematuria or pneumaturia. Imaging tests, such as abdominal ultrasound or pelvic CT should be considered in the case of urinary tract stones and its risk factors, including Proteus, as well as in the case of hematuria or suspected obstruction. Uroflowmetry may be an adjunct tool with a history of urinary incontinence. If symptoms persist and urine culture is negative, differential diagnosis and other causes should be considered, for example atypical pathogens, gynecological causes (vaginal atrophy, endometriosis), interstitial cystitis, anatomical abnormalities (diverticula, stenoses), drug side effects and cancer. Particularly noteworthy is interstitial cystitis[[23]](#endnote-23). Particularly noteworthy is interstitial cystitis, also called painful bladder syndrome. It manifests itself with a frequent and urgent need to urinate and pain in the suprapubic area. It often co-occurs with chronic pain syndromes, as well as conditions related to dysregulation of the autonomic system, e.g. Raynaud's syndrome. Both IC and Raynaud's syndrome are caused by inflammation and changes in neurochemical transmission[[24]](#endnote-24).

Research is currently underway to establish biomarkers that will be more accurate in the diagnosis of rUTI[[25]](#endnote-25). As for factors present in the blood, it turned out that women with rUTI had higher levels of IgA, IgM, IgG. Among women of reproductive age, vitamin D levels were significantly reduced in the rUTI group compared to the healthy population[[26]](#endnote-26).

Vitamin D participates in the regulation of homeostasis, among others. by influencing the cardiovascular system, as well as modulating inflammatory processes related to innate and acquired immunity[[27]](#endnote-27) [[28]](#endnote-28). An important element is influencing neutrophil function. In turn, among the biomarkers present in urine, Nerve Growth Factor (NGF) was described and its reduced level was correlated with rUTI. NGF is a protein from the neurotrophin family and participates in the initiation of nerve growth and differentiation. Its increased amount was observed in women with overactive bladder. In cases of asymptomatic recurrent infections, attention was drawn to the correlation between increased IL-8 levels and bacteriuria and neutrophilia in peripheral blood[[29]](#endnote-29).

**2.3. Treatment**

Therapeutic treatment for rUTI should be multi-level[[30]](#endnote-30). In addition to antibacterial drugs, risk factors should be combated, lifestyle modifications and antimicrobial prophylaxis should be introduced. In acute infection, the first line of treatment is empirical antibiotic therapy lasting a maximum of 7 days. In case of recurrence, urine culture should be performed before starting treatment. The choice of medication should take into account local differences of antibiotic resistances. Antibiotics used for rUTI are the same as for sporadic uncomplicated UTI. According to EAU guidelines, well-educated patients who follow the recommendations should implement self-diagnosis and self-treatment[[31]](#endnote-31). This strategy is recommended when <4 episodes of UTI have occurred in a year. If symptoms are unusual or have not improved 48 hours after starting treatment, the patient should see a doctor. The table below shows the treatment regimen for uncomplicated cystitis established by the EAU (2022).

*Tab. 1 Suggested regimens for antimicrobial therapy in uncomplicated cystitis****25***

|  |  |  |  |
| --- | --- | --- | --- |
| Antimicrobial | Daily dose | Duration of therapy | Comments |
| **First-line women** |
| Fosfomycin trometamol | 3 g single dose; | 1 day | Recommended only in women with uncomplicated cystitis. |
| Nitrofurantoin macrocrystal | 50-100 mg four times a day | 5 days |
| Nitrofurantoin monohydrate/macrocrystals | 100 mg twice daily; | 5 days |
| Nitrofurantoin macrocrystal prolonged release | 100 mg twice daily; | 5 days |
| Pivmecillinamb | 400 mg three times daily | 3-5 days |
| **Alternatives** |
| Cephalosporins(e.g. cefadroxil) | 500 mg twice daily; | 3 days | Or comparable |
| **If the local resistance pattern for E. coli is < 20%** |
| Trimethoprim | 200 mg twice daily; | 5 days | Not in the first trimenon of pregnancy |
| Trimethoprim-sulfamethoxazole | 160/800 mg twice daily; | 3 days | Not in the last trimenon of pregnancy |

a*do not use if you suspect pyelonephritis (due to poor tissue penetration) or GFR is <30 ml/min/m2.*

*bdo not use if you suspect pyelonephritis (due to poor tissue penetration)*

When it comes to empirical therapy, the use of aminopenicillins is not currently recommended. By virtue of global resistance to E. coli, they have low effectiveness, and when combined with a beta-lactamase inhibitor (e.g. sulbactam or clavulanic acid), the side effects outweigh the therapeutic effect. It is worth mentioning that in 2019 the European Commission developed strict guidelines aimed at limiting the use of fluoroquinolones due to their harmfulness and long-term side effects. In cystitis, fluoroquinolones are used as a last resort when the use of other drugs is invalid.

**2.4. Prophylaxis**

**2.4.1 Non-pharmacological and non-antibiotic methods**

In some patients, rUTI may be caused by inappropriate habits or insufficient hygiene. Although the evidence for the effectiveness of behavioral modifications is limited, patients should be educated and aware of risk factors[[32]](#endnote-32). It's worth promoting health-promoting behaviors such as physiological posture during urination, wiping from front to back, urinating after intercourse, avoiding long baths, avoiding using spermicides, washing hands before washing intimate parts, using mild cleansers, emptying the bladder regularly, using tampons instead of sanitary pads during menstruation, wearing airy underwear and non-tight clothes. In specific groups of patients, increased water consumption > 2 liters per day may be beneficial[[33]](#endnote-33).

A popular claim rooted in the medical community was the effect of cranberries on reducing the incidence of infections. It was believed that the proanthocyanidins (PACs) contained in cranberries reduce the adhesion of bacteria to the uroepithelium. A meta-analysis was conducted, with a double-blind placebo trial, which confirmed that the use of cranberries does not reduce the risk of disease compared to placebo. Moreover, cranberry preparations available on the market contain large amounts of sugar and should not be used by diabetics[[34]](#endnote-34).

The next target of treatment were bacterial pili, which, thanks to the presence of sugar residues, enable adhesion to host cells. D-mannose molecules were supposed to limit the adhesion of bacteria by competitive inhibition, but they had low effectiveness. More optimistic results were provided by mannosides, analogues of D-mannose. Thanks to their compatible spatial structure, they inhibit bacterial adhesion 10 times more effectively than D-mannose, and have higher bioavailability and half-life[[35]](#endnote-35).

There is also inconclusive evidence of effectiveness regarding methenamine hippurate, a substance that is supposed to lower urine pH. It should not be used when GFR is <10 ml/min/m2.

Intrabladder administration of glycosaminoglycans (hyaluronic acid/chondroitin) reduces bacterial adhesion and supports the regeneration of the uroepithelium. Thanks to this, it has been used in the treatment of interstitial cystitis, radiation-induced cystitis and overactive bladder[[36]](#endnote-36).

Both EAU and AUA/CUA/SUFU recommend vaginal estrogen therapy for all peri- and postmenopausal women unless there are contraindications to the use of this hormone[[37]](#endnote-37).

Local use of estrogen has higher effectiveness and fewer side effects compared to systemic therapy. Although an increased risk of breast cancer has not been demonstrated in women with a history of breast cancer, estrogen should be used after consultation with an oncologist[[38]](#endnote-38).

EAU guidelines recommend immunoprophylaxis with OM-89 (Lyophilized E. coli lysate) administered orally. This extract strengthens the host's immune system by stimulating the production of cytokines and antibodies

**2.4.2 Pharmacological methods**

Numerous meta-analyses have shown that the most effective method of rUTI prevention is continuous or postcoital antibiotic prophylaxis[[39]](#endnote-39). This method should be considered when non-antibiotic methods of prevention are used and potential side effects should be remembered, such as the risk of increased resistance or gastrointestinal disorders. The golden standard is the so-called long protocol lasting 6-12 months, according to which the patient takes the medicine daily or several times a week. The drug is selected based on the medical record, and after 3 months a preliminary assessment of effectiveness is made. Postcoital prophylaxis is preferred in young sexually active patients. This is associated with fewer adverse effects from medications. Prophylactic doses are lower than therapeutic doses and are presented in the table below.

*Tab. 2 Suggested regimens for antimicrobial prophylaxis for rUTI****25***

|  |  |  |
| --- | --- | --- |
| **Antimicrobial agents** | **Continuous prophylaxis (daily dose) (mg)** | **Postcoital prophylaxis (one-time dose) (mg)** |
| Cephalexin | 125-250 | 250 |
| Fosfomycin | 3000 every 10 days | - |
| Nitrofurantoin | 50-100 | 50-100 |
| Trimethoprim/sulfamethoxazole | 40/200 daily Or thrice weekly | 40/200-80/400 |

Due to the global increase in the number of multidrug-resistant strains, antibiotics are becoming less and less effective. Innovation and a complete change in treatment lines are necessary[[40]](#endnote-40). In the future, non-antibiotic methods will be the main therapeutic tools. Great hopes are associated with the activities of the Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium financed by the National Institutes of Health[[41]](#endnote-41). Scientists from this association work on targeted vaccines against pathogens, modification of the host response by NSAIDs and the use of mannosides. There are also promising results of research on biofilm destruction by biodegrading enzymes such as alginate lyase, DNase, substances inhibiting the expression of genes encoding fimbriae such as Sitagliptin and prazosin, and competitive inhibition mechanisms involving S-adenosylmethionine[[42]](#endnote-42)**.**

**3.** **Conclusions:**

In the era of global antibiotic resistance, rUTI may be a significant problem. While treating acute infections is usually not difficult, it is difficult to prevent recurrences.

Chronic antibiotic therapy significantly reduces the quality of life of patients and is associated with numerous side effects and dysbiosis. Frequent relapses and the need for long-term antibiotic therapy reduce the quality of life and may even lead to mental disorders such as depression. Due to the complexity of the problem, separate pathomechanisms, and pathogen-host interactions, rUTI should be perceived as a separate disease entity. In each case, individual risk factors should be considered, holistic treatment and prevention should be taken into account. This will make it possible to limit the amount of antibiotics usage, reduce the antibiotic resistance and the number of new infections.

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