REVIEW

# Recent advances in managing lower urinary tract infections [version 1; referees: 2 approved]

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## Abstract

Urinary tract infections (UTIs) are among the most common bacterial infections. Traditionally, all symptomatic UTIs are tested and treated. The use of antibiotics has resulted in an antibiotic resistance crisis, and we have limited options for managing UTIs. Currently, we live in the era of antimicrobial resistance and may live in other eras like the era of the microbiome. New insights might provide an opportunity to prevent the overuse and misuse of antibiotics and could enable the development of innovate managing strategies.

## Keywords

Urinary tract infections, antimicrobial resistance, microbiome

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## Introduction

The world is changing rapidly; there is hardly anything in life that is not changing. Technological advancements have enriched our lives, but others have created fear and anxiety. The number of antibiotic-resistant pathogens is rapidly increasing, and many pathogens are becoming multidrug resistant (MDR) with the attendant increased risk of failure of standard therapies[1]. Several decades ago, the first antibiotic saved our lives from bacterial infection, but now bacterial infections have again become a threat. The overuse and misuse of antibiotics, along with the development of few new drugs by the pharmaceutical industry, are the most important causes of the antibiotic resistance crisis[2].

Urinary tract infections (UTIs) are among the most common bacterial infections managed by clinicians[3]. Traditionally, a UTI is defined as microbial infiltration of the normally sterile urinary tract, and most clinicians think all symptomatic UTIs should be treated[4,5]. Recently, however, the paradigm for the management of infectious diseases started to shift as the concept of the microbiome has been established[6].

## Stop the overuse and misuse of antibiotics

Asymptomatic pyuria and bacteriuria are very common in the elderly, especially in women residing in long-term care facilities or in patients who use a urinary catheter, with a prevalence of 25–50%[7,8]. In older residents of long-term care facilities, diagnostic testing and the initiation of antibiotics should be reserved for residents with fever, dysuria, gross hematuria, worsening urinary frequency and incontinence, costovertebral angle tenderness, or suspected bacteremia. Non-specific symptoms and altered mental status are no longer part of the recommended evaluation for a possible UTI[9,10]. Asymptomatic bacteriuria also occurs in an estimated 1–5% of healthy pre-menopausal females, increasing to 0.7–27% of patients with diabetes, 2–10% of pregnant women, and 23–89% of patients with spinal cord injuries[11,12]. Asymptomatic bacteriuria does not cause systemic disorders, such as renal damage[13]. Thus, the treatment of asymptomatic bacteriuria is not recommended in patients without risk factors[11]. Avoiding antibiotic administration in cases where the urine culture does not indicate UTI may be the first step to decreasing antibiotic misuse[14].

For patients with non-febrile uncomplicated UTIs, active pain control and minimal use of antibiotics should be prioritized. Uncomplicated cystitis can be a self-limiting disease in some cases. Pain in acute cystitis is a natural consequence of the inflammatory response, and pain-mediated urinary frequency or urgency is the chief complaint of patients. Therefore, for this self-limited disease, painkillers, including NSAIDs, may be a good option for symptomatic care as well as reducing the consumption of antibiotics[15,16]. Delaying antibiotic treatment with a back-up prescription to see if symptoms will resolve without antibiotic treatment, or delaying the antibiotic until microbiological results are available, may be an option for antibiotic sparing[17].

Recently, multiplex PCR assays for the detection of sexually transmitted infection (STI) agents became commonplace in Eastern Europe, Western Europe, South America, and Asia[18–20]. However, the use of unnecessary antibiotics has increased by including strains other than "true" STIs such as *Mycoplasma hominis*, *Ureaplasma urealyticum* (previously *U. urealyticum* biovar 2), and *Ureaplasma parvum* (earlier *U. urealyticum* biovar 1)[21]. *M. hominis*, *U. urealyticum*, and *U. parvum* are commonly detected in the urogenital tract of both healthy and symptomatic individuals[22,23]. Testing for *M. hominis* and *U. parvum* and subsequent antimicrobial treatment of positive men or women are currently not recommended. Instead, "true" STIs and bacterial vaginosis in symptomatic women should be diagnosed and treated[21]. Bacterial vaginosis, sexually transmitted diseases (STDs), and pelvic inflammatory disease can mimic symptoms of UTIs. In fact, a recent study showed that approximately one-third of STD cases were misdiagnosed as UTIs[24].

## The era of antimicrobial resistance

There are limited oral options for the treatment of antibiotic-resistant uropathogens associated with lower UTIs (acute cystitis). Co-trimoxazole was a typical antibiotic used to treat UTIs, but the resistance of *Escherichia coli* to this drug has markedly increased. According to the literature published in the past decade, the resistance rates of *E. coli* to co-trimoxazole varied but were usually over 15–30%[25–28]. However, there was an interesting report wherein the authors emphasized the role of co-trimoxazole in empirical antibiotics because of the recent decrease in the resistance rate to co-trimoxazole in several European countries owing to its low prescription rate[29]. Nevertheless, it may not be possible to reuse the drug worldwide within the next few years, and close observation of surveillance data will be required.

With respect to fluoroquinolones, the increase of resistance in uropathogens has occurred at an alarming rate in relation to increased prescribing practices[27,28]. Fluoroquinolones are no longer recommended as first-line therapy for uncomplicated UTIs[11]. Similar to what was seen with co-trimoxazole, there is evidence that escape from exposure to this antibiotic will increase antimicrobial susceptibility in UTIs. According to Lee *et al.*, the susceptibility of Gram-negative bacteria to ciprofloxacin was much higher in patients younger than 20 years old than in patients older than 20 years old. The reason for this observation may be the lower exposure to fluoroquinolones in young individuals because these drugs are not recommended for use in those under 20 years old[30].

One recent issue of importance is the increasing prevalence of extended spectrum beta lactamase (ESBL)-producing uropathogens. Before 2010, the vast majority of countries showed less than a 5–10% prevalence of ESBL-producing *E. coli*, whereas the prevalence exceeded 10% in the local communities of many countries after 2010[31–35]. Therefore, the increase in ESBL-producing *E. coli* is no different to that of co-trimoxazole-resistant *E. coli* or fluoroquinolone-resistant *E. coli*, and the prevalence of ESBL-producing *E. coli* is likely to increase soon.

## Use of re-emerging older antibiotics

Fosfomycin is an oral antibiotic agent that has broad activity against MDR uropathogens including ESBL-producing *E. coli*. Fosfomycin prevents peptidoglycan synthesis earlier than do

beta-lactam or glycopeptide antibiotics and is broadly active against several Gram-positive and Gram-negative organisms, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* spp.. Fosfomycin has been shown to have advantages in the treatment of UTIs owing to its high concentration in the urinary tract, which exceeds 2,000 mg/L after the initial administration and remains at high levels for a prolonged period, over 24 hours. However, oral fosfomycin should not be used for pyelonephritis or in patients with bacteremia because of inadequate concentrations within the bloodstream[36,37]. Fosfomycin susceptibility in uropathogens, including *E. coli*, is currently greater than 90%, even in ESBL-producing *E. coli*[38–40]. It is safe to use in pregnancy[41]. The drug is likely to be excreted in low levels in breast milk, but would not be expected to cause any adverse effects in breastfed infants, especially if the infant is older than two months.[42].

Another oral antimicrobial agent that can be considered for the treatment of ESBL-producing *E. coli* cystitis is nitrofurantoin. Nitrofurantoin is a drug that has been used since the 1950s to treat uncomplicated UTIs and works by damaging bacterial DNA in its highly active reduced form. Now, and even in earlier eras of widespread use, the baseline resistance to nitrofurantoin is low (0–10%)[43,44]. Nitrofurantoin should be used only for lower UTIs, and its use should be avoided in patients with a creatinine clearance of less than 60 mL/minute, as reduced renal function results in decreased active drug within the urine[45]. Nitrofurantoin is one of the few drugs that can be used during pregnancy[46]. A recent retrospective, matched-cohort study in older adults concluded that long-term use of nitrofurantoin is associated with greater risk of lung injury than acute exposure[47].

## Role for non-antimicrobial prophylaxis

The active use of non-antimicrobial prophylaxis is often indicated and does not result in an increase in antimicrobial resistance of the commensal flora. Immunoactive agents, probiotics (*Lactobacillus* spp.), cranberry-based products, D-mannose, methenamine hippurate, hormonal replacement (in post-menopausal women), and other options have been studied as non-antimicrobial prophylaxis[48–53]. Evidence for the use of non-antimicrobial prophylaxis is hampered by considerable heterogeneity, and further placebo-controlled randomized trials of these agents are needed. However, trials investigating these options have produced promising results and combining these agents may offer the best route to lowering the rate of recurrent UTIs without needing to use antimicrobials[54].

Among these modalities, the urinary immunopotentiator is now well documented and strongly recommended in the guidelines[11]. The oral immunostimulant OM-89 (Uro-Vaxom®), an extract of 18 different serotypes of heat-killed uropathogenic *E. coli*, stimulates innate immunity by increasing non-specific and specific humoral and cellular immune responses via the induction of interferon-γ and tumor necrosis factor-γ production as well as the activities of lymphocytes and macrophages[55–57]. Uro-Vaxom® is a safe and effective medicine that can reduce recurrent UTI episodes[48,58–60] and can effectively reduce the repeated use of antibiotics[61]. Uromune® is a sublingual spray consisting of equal amounts of four common UTI-causing bacteria in a suspension of $10^9$ inactivated whole bacteria/mL: *E. coli*; *Klebsiella pneumoniae*, *Proteus vulgaris*, and *Enterococcus faecalis*[54]. The data from European prospective and retrospective studies suggest that Uromune® is a viable alternative therapy for treating recurrent UTIs in women[62,63].

The lower estrogen state found in postmenopausal women is linked with decreased innate immunity via the loss of the commensal bacteria *Lactobacillus* and the loss of the acidic pH microenvironment within the vagina. Although specific mechanisms are still poorly understood, estrogen plays a key role in modulating the natural defense of the lower urinary tract against UTIs[64]. The role for topical (intravaginal cream, vaginal rings, impregnated pessary rings, vaginal pessaries, and vaginal tablets) estrogen in averting recurrent UTIs in postmenopausal women compared with placebo is clear, and guidelines for this population recommend their use[11,65,66]. Currently, there is evidence that $CO_2$ ablative vaginal lasers may help rejuvenate this microenvironment, much like topical estrogen therapy, restoring the lactic acid synthesis of commensal bacteria and the innate vaginal defense against UTIs[67–69]. For postmenopausal women, vaginal estrogen therapy has been considered often as an adjunct to antimicrobial-based prophylaxis[70]. However, combination therapy with both immunostimulants and vaginal therapy (laser rejuvenation or estrogen) may provide better effectiveness at preventing UTI recurrence in postmenopausal women and is a potentially novel avenue for further research.

## Paradigm shifting in the era of the microbiome

The microbiota is defined as the microorganisms in a particular environment. The microbiome refers to their genomes that are revealed using molecular techniques such as 16S ribosomal RNA (rRNA) sequencing[71]. Recently, more sensitive diagnostic tests demonstrated that urine is not sterile[72]. The urinary tract is inhabited by a unique urinary microbiota, and standard bacteriuria represents a fraction of the diverse microbiota hosted by the urinary tract[73]. In the past, the notion that UTI was the detection of organisms as a standard culture in sterile urine has changed in the era of the microbiome. The fact that we diagnosed UTIs through standard culture and antibiotic susceptibility ignored the dozens of bacterial species and intracellular bacterial colonies known to reside in the urinary tract[72]. As expected, in the era of the microbiome, stable bacterial communities are generally beneficial and this condition is referred to as symbiosis. In this sense, patients with urinary tract symptoms would be more likely to be classified as having urinary tract dysbiosis rather than a UTI[73]. If the full array of microbes resident in the human urinary tract is identified in the near future, some treatment of UTIs by antibiotics may turn into a correction of dysbiosis. In the gut microbiome, treatments of *Clostridium difficile* infections through fecal transplants have been investigated[74,75]. In the urinary tract, the instillation of non-pathogenic *E. coli* safely reduced the risk of symptomatic UTI in patients with spinal cord injury. All of these efforts are ultimately related to preventing

the overuse and misuse of antibiotics. The paradigm of managing UTIs has shifted from diagnosing UTIs and antibiotic treatment to screening for patients who really need antibiotics.

## Conclusions

A clear achievement in recent oncology is the emergence of immunotherapy, a type of treatment that helps our immune system fight cancer and that marks an entirely different way of treating cancer by targeting the immune system, not the tumor itself. If the immune system also helps our body fight infections, why not use our body's immune system instead of antibiotics to treat UTIs? This paradigm shift seems to be beginning in the management of UTIs. Further understanding of the microbiome in the urogenital system is expected to stimulate this shift. Eventually, the spread of antibiotic resistance can be reduced if antibiotics are used only when they are needed.


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Version 1

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