Dealing With Recurrent Urinary Tract Infections: Current Approaches

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Recurrent Urinary Tract Infections: A Growing Menace

Urinary tract infections (UTIs) are amongst the most common infectious diseases in community practice.[1] UTIs are caused by both Gram-negative and Gram-positive bacteria.[2] *Escherichia coli* remains the predominant uropathogen (80%) isolated, followed by *Staphylococcus saprophyticus* (10-15%). Klebsiella, Enterobacter, Streptococcus, Serratia, Enterococci, and Proteus species account for the remaining 5-10% of UTIs.[3-5] It should be noted that colonization of uropathogens may involve lower as well as upper urinary tract. The infections of the lower urinary tract include cystitis, urethritis, prostatitis, and epididymitis, and those of the upper urinary tract include pyelonephritis.[6] The clinical features of UTIs most commonly include urinary frequency, urgency, dysuria, suprapubic pain, and possible hematuria (Table 1).[7,8]

Table 1: Clinical features of urinary tract infections

Lower UTI (cystitis, urethritis)	Upper UTI (pyelonephritis)
• Urinary frequency • Urinary urgency • Suprapubic pain • Dysuria • Hematuria	• Fever, chills • Flank pain • Nausea, vomiting • Costovertebral or renal angle tenderness • Symptoms of lower UTI which are recurrent

Recurrent UTIs are defined as having more than two infections in a 6-month period, or 3 infections within the preceding 12 months, with complete resolution for at least two weeks.[7,9] Recurrent UTIs may occur due to relapse (symptomatic recurrent UTIs with the same organism after adequate therapy) or reinfection (recurrent UTIs with previously isolated bacteria after treatment and with a negative intervening urine culture, or a recurrent UTI caused by a different pathogen). In conditions where the same pathogen is isolated, distinction between relapse and reinfection becomes challenging. It is supposed that most recurrent UTIs represent reinfection with the same organism.[7,10] Herein, it should be noted that reinfection accounts for 80-95% of recurrent UTIs in women.[11,12] Approximately 30-44% of women who have an episode of UTI are supposed to have a recurrence, often within three months. Observational cohort studies have revealed a recurrence rate of 0.3-7.6 infections per patient per year, with an average rate of 2.6 infections per year.[13] Besides, available data from primary care setting suggest that 53% of women older than 55 years and 36% of younger women experience a recurrence within one year. Recurrent UTIs, frequently observed in otherwise healthy young women with anatomically and physiologically normal urinary tracts, are a major healthcare concern.[9,10]

Risk Factors for Recurrent UTIs

There are several risk factors for recurrent UTIs including an impairment of the body's immune system and virulence factors.[7] The strongest risk factor for recurrent UTIs in sexually-active premenopausal women is frequency of sexual intercourse. Besides, the use of spermicides for contraception, the age of the first UTI, and a maternal history of UTI are some of the other important risk factors. An increased postvoid residual urinary volume (> 50 mL) is an independent risk factor for recurrent UTIs in postmenopausal women.[8,11,12]

Managing Urinary Tract Infections in the Era of Antimicrobial Resistance

Antimicrobial therapy plays a major role in the management of urinary tract infections. However, it has been evident that empirical antimicrobial treatment is initiated in most of the cases before the laboratory results of urine culture are obtained. This frequent misuse of drugs has significantly contributed to the rising problem of antimicrobial resistance, which has made the treatment complicated and challenging.[1,14-16] It has been reported that *E. coli*, the most commonly implicated pathogen in urinary tract infections has become resistant to several antibiotics including fluoroquinolones, trimethoprim/sulfamethoxazole, penicillins, and cephalosporins.[17-19] In fact, according to the WHO's 2014 global report on antibiotic resistance, which provides comprehensive antibiotic resistance data from 114 countries, *E. coli* resistance to fluoroquinolones is so widespread that in many parts of the world this treatment is now ineffective in more than half of the patients. The WHO report further shows high levels of *E. coli* resistance to third generation cephalosporins as well, including in South-East Asia Region, which is home to a quarter of the world's population.[20] Thus, the rising antimicrobial resistance mandates the need for an optimal therapeutic agent. Selection of such an agent must take into account local resistance patterns, patient-specific factors, including anatomic site of infection and severity of disease, pharmacokinetic and pharmacodynamic principles.[17,21,22] In context to this, nitrofurantoin has emerged as a drug of choice, with good efficacy and favorable tolerability profile.[19,23]

Contribution of Nitrofurantoin in Combating Urinary Tract Infections

Nitrofurantoin has a unique mechanism of action; it mainly acts by inhibiting various bacterial enzymes that participate in bacterial carbohydrate metabolism at three different locations in the Krebs cycle. In addition, it also interferes with cell wall synthesis. The nitro group coupled onto the heterocyclic furan ring represents the specific active site of the drug that has to be activated by microbial nitroreductases to form bactericidal end-products, which bind to deoxyribonucleic acid (DNA) and protein with consequent inhibition of nucleic acid synthesis. To summarize, it acts by undergoing reduction by bacterial nitroreductases to produce toxic derivatives that attach to ribosomal proteins and cause defective transcription and translation in bacteria.[24-27] Furthermore, the pharmacokinetic properties such as pH dependent resorption at normal urinary pH (approximately 5.5 pH); excretion primarily into the lower urinary tract, i.e., bladder urine, renders it a beneficial agent in the treatment of urinary tract infections.[25] In addition, this drug displays advantages in terms of site specificity and attainment of high urinary levels. It is rarely associated with any adverse events, thus presenting an excellent tolerability profile. Another property of this drug that makes it a suitable agent in the management of urinary tract infections is minimal resistance to pathogens.[24,28]

Antimicrobial Spectrum of Nitrofurantoin

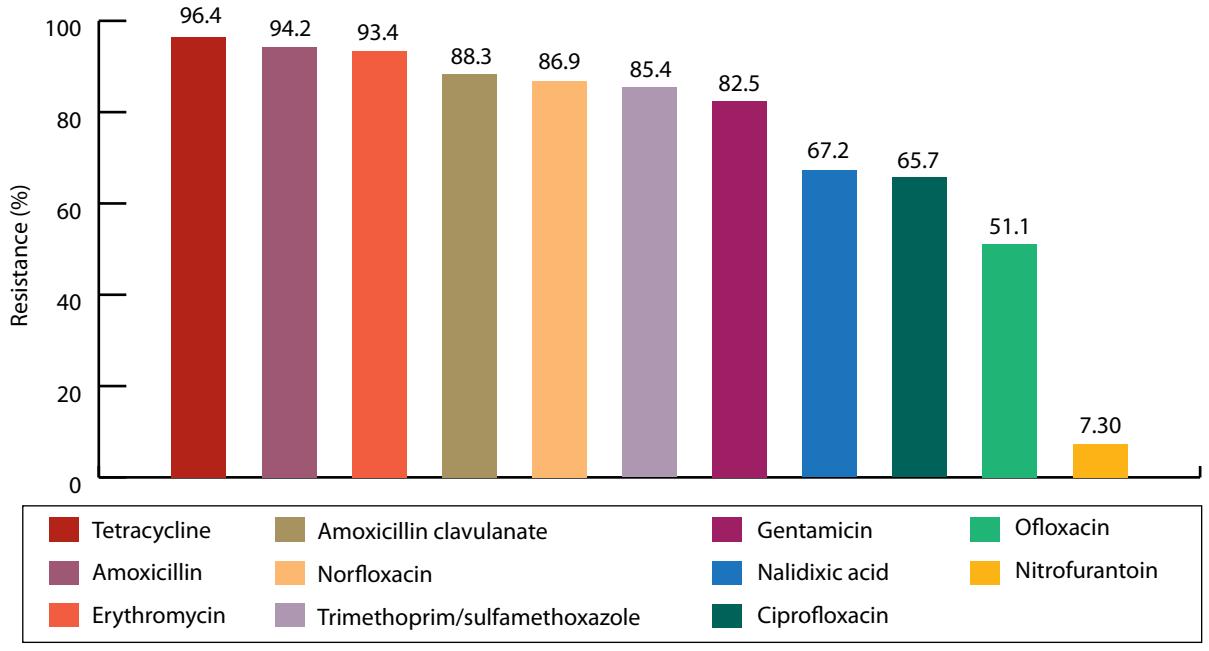
The antibacterial spectrum of nitrofurantoin is broad and the drug is particularly effective against the main uropathogens. Nitrofurantoin is active against *E. coli*, Enterococci, *S. aureus*, *Klebsiella pneumonia*, Enterobacter species, Citrobacter species, group B Streptococci and most strains of multidrug-resistant Gram-negative bacilli.[25,29,30] Nitrofurantoin is gaining prominence in the management of UTIs due to increasing incidence of resistance against other commonly used antibiotics, such as trimethoprim/sulfamethoxazole (TMP/SMX), resulting in treatment failures.[29] Interestingly, a study by Olorunmola and coworkers[31] revealed high sensitivity of nitrofurantoin in comparison with other antibiotics to *E. coli* isolates from cases of UTI. The findings revealed widespread resistance of the isolates to all the antibiotics (51.1-96.4%), except nitrofurantoin that showed a low resistance rate of 7.3% (Figure 1).

Similar outcomes have also been reported from studies conducted in Indian patients with urinary tract infections. The investigators of one such study[32] demonstrated that *E. coli* was the most frequently isolated microbe accounting for 61.84% of the total isolates. Moreover, majority of *E. coli* strains were resistant to various antibiotics such as ampicillin (>80%), amoxiclav (>80%), co-trimoxazole (>67%), nalidixic acid (>95%), norfloxacin (>77%), and ciprofloxacin (>74%). However, nitrofurantoin was reported as the drug with least resistance (>5-6%) to *E. coli* throughout the study duration of 30 months.

Evidence-based Efficacy of Nitrofurantoin in Patients with Urinary Tract Infections

Data available from several studies provides evidence in favor of the efficacy of nitrofurantoin in the management of UTIs. In a study by Kumar and coworkers,[18] nitrofurantoin

Figure 1: Resistance of Escherichia coli to different antibiotics

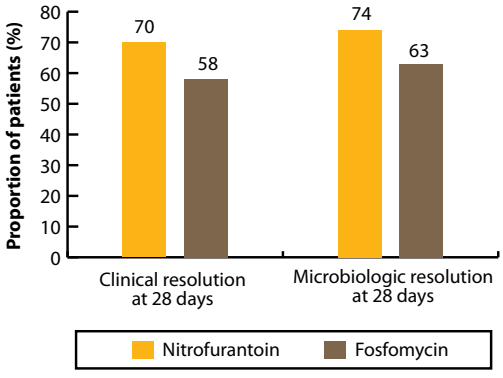


displayed sensitivity to about 90.9% of the *E. coli* isolates from patients with urinary tract infections.

A comparative study[33] assessed the clinical and microbiologic efficacy of oral nitrofurantoin, 100 mg 3 times a day for 5 days and a single 3-g dose of oral fosfomycin in women with uncomplicated UTI treated for 28 days. The results demonstrated that clinical resolution at 28 days occurred in 70% of patients in the nitrofurantoin group versus 58% of patients in the fosfomycin group. Likewise, microbiologic resolution occurred in 74% versus 63%, respectively (Figure 2). It could thus be concluded that five-day nitrofurantoin may be a better alternative to single-dose fosfomycin for treating uncomplicated UTI in women.

In another study[34] involving 60 patients presenting with acute/uncomplicated or recurrent UTI at a tertiary care center in India, a remarkable difference was observed between post-treatment urine culture results of patients treated with nitrofurantoin versus those treated with ciprofloxacin. Post-treatment growth of uropathogen was observed in 16.67% of cases in nitrofurantoin group as compared to 46.67% of cases in ciprofloxacin group (Figure 3). Since a positive urine culture is suggestive of less effective treatment, it could be concluded that nitrofurantoin is more efficacious than ciprofloxacin in

Figure 2: Clinical and microbiologic outcomes with nitrofurantoin versus fosfomycin therapy in patients with urinary tract infections



the treatment of acute/uncomplicated or recurrent UTI. Thus, it can be stated that while *E. coli* remains the most common causative pathogen in infections of urinary tract, nitrofurantoin continues to be the most effective drug for the management of the same.[35]

Nitrofurantoin: Benefits in Recurrent Urinary Tract Infections

Strategies to prevent recurrent UTIs include low-dose antimicrobial prophylaxis over long term or postcoital

Figure 3: Culture results after treatment with nitrofurantoin versus ciprofloxacin in patients with urinary tract infection

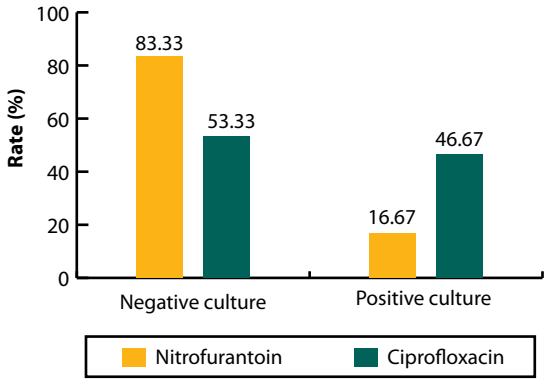
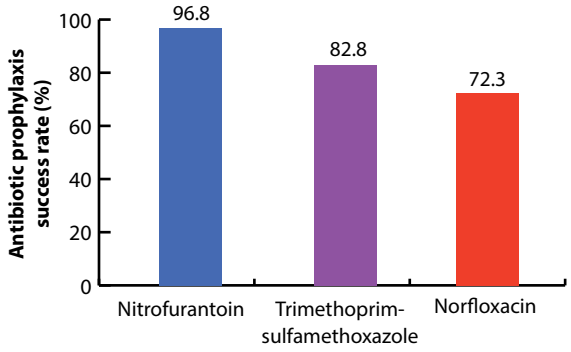


Figure 4: Prophylaxis success rate with different antibiotics in patients with recurrent urinary tract infections



antibiotic treatment in premenopausal women.[36] Nitrofurantoin is a good option for long term prophylaxis of lower UTIs as it is effective, and well-tolerated with few adverse effects. It has been recommended at a dose of 50 mg at night for a period of 12 months to prevent recurrence of UTI.[37] Alternatively, post-coital prophylaxis involving early bladder voiding and nitrofurantoin (50 or 100 mg single tablet), has also been found effective in preventing recurrence of UTI.[38] In a study[39] involving 181 women with recurrent UTI undergoing treatment for ≥6 months, the most effective regimen for antibiotic prophylaxis was nitrofurantoin with a success rate of 96.8% compared with 82.8% for TMP/SMX and 72.3% for norfloxacin, thus substantiating nitrofurantoin as the most potent among the administered therapeutic agents (Figure 4). Importantly, nitrofurantoin is also shown to be useful in patients with diabetes as they are at increased risk of severe, recurrent UTIs.[40] A study[41] on 105 women, aged 50-70 years, with diabetes and recurrent UTIs, demonstrated that nitrofurantoin is effective in both prophylaxis and treatment of recurrent UTIs in women with diabetes.

Nitrofurantoin, owing to its clinical efficacy, minimal resistance to uropathogens, and minimal propensity for collateral damage, has been recommended by several international guidelines (National Institute for Health and Clinical Excellence, Infectious Diseases Society of America, European Association of Urology, and Canadian Urological Association) as a first line drug for the treatment of urinary tract infections. Use of nitrofurantoin has also been recommended by some textbooks like Campbell-Walsh Urology and Nelson Textbook of Pediatrics, as summarized in Table 2.[24,42-47]

Recurrent Urinary Tract Infection in Pregnancy

UTI is considered the most frequent medical complication of pregnancy. As recurrent UTIs are common in pregnancy, they require prophylactic treatment if they occur.[8] For pregnant women with symptomatic or asymptomatic UTI, the risk of a preterm delivery and low birth weight infant is markedly increased.[9] Screening for UTI is recommended in all pregnant women at their first prenatal visit and then in the third trimester.[8] Indications for prophylaxis are; all women with a pre-pregnancy history of recurrent UTIs, unrelenting symptomatic or asymptomatic bacteriuria after two antibiotic treatments, and after only one UTI for a woman who has other conditions, such as diabetes, that may increase the risk of urinary complications during the episode of UTI. Both continuous and post-coital prophylaxis regimens have been shown to be effective, and nitrofurantoin is among the therapeutic agents of choice for pregnant women with recurrent UTI.[8,9]

Modified Release Nitrofurantoin

Modified release formulation should be preferred over conventional and sustained release formulations, as modified release nitrofurantoin provides release of initial loading dose in beginning to achieve desired MIC levels. This is followed by release of maintenance dose, which releases constantly over period of time to maintain adequate urinary concentration. Loading dose ensures no

Table 2: Recommendations on the use of nitrofurantoin	
Books/Guidelines	**Comments/Recommendations**
Campbell-Walsh Urology	• Nitrofurantoin is a suitable option to be used in pregnant women who are allergic to penicillin • The authors have suggested that nitrofurantoin has developed least antimicrobial resistance over a period of 5 years as compared to trimethoprim/sulfamethoxazole, ampicillin, and cephalothin
Nelson Textbook of Pediatrics	• It is effective in the treatment of lower urinary tract infections such as acute cystitis caused by Gram-positive and Gram-negative pathogens.
NICE Guideline 2018 Urinary Tract Infection (Recurrent): Antimicrobial Prescribing	• Antibiotic prophylaxis » Adults and young people aged ≥16 years ◆ First choice: Nitrofurantoin (if eGFR ≥45 ml/minute) ◆ Dosage: 50 to 100 mg single dose or 50 to 100 mg at night continuously » Children and young people < 16 years ◆ First choice: Nitrofurantoin (if eGFR ≥45 ml/minute) ◆ Dosage: 3 months to 11 years, 1 mg/kg at night; 12 to 17 years, 50 mg to 100 mg at night
EAU Guidelines on Urological Infections 2018	• Uncomplicated cystitis in adults » Nitrofurantoin macrocrystal, 50-100 mg four times a day for 5 days (only in women with uncomplicated cystitis) » Nitrofurantoin monohydrate/ macrocrystals, 100 mg twice daily for 5 days » Nitrofurantoin macrocrystal prolonged release, 100 mg twice daily for 5 days • Cystitis in pregnancy (not in case of G6P deficiency and during end of pregnancy) » Short courses of antimicrobial therapy with nitrofurantoin • Adults with recurrent UTIs » Continuous antimicrobial prophylaxis with nitrofurantoin (macrocrystal) 50 mg or 100 mg once daily
IDSA 2011*	• Acute uncomplicated cystitis and pyelonephritis » Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for 5 days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage and efficacy comparable to 3 days of trimethoprim-sulfamethoxazole
Canadian Urological Association Guideline 2011	• Recurrent UTI: Prophylaxis » Nitrofurantoin (50 mg to 100 mg): Continuous » Nitrofurantoin (50 mg–100 mg daily) : Postcoital (within 2 hours of coitus)
Abbreviations: eGFR, estimated glomerular filtration rate; EAU, European Association of Urology; IDSA, Infectious Diseases Society of America; NICE, National Institute for Health and Clinical Excellence; UTI, urinary tract infection. * International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases	

risk of treatment failure. It has been seen that modified release nitrofurantoin formulation provides better GI tolerance when compared to conventional and plain nitrofurantoin tablets. Advantages of modified release nitrofurantoin are discussed in Box 1.[18]

Adjuvant Measures

Managing Painful/Burning Micturition: Focus on Potassium Citrate

It has been found that burning micturition constitutes the most common distressing feature reported in patients with UTI. A study[48] conducted among 139 females aged ≥15 years revealed the same, wherein burning micturition (73.4%) was the most prevalent symptom reported by the participants, followed by frequency (43.9%), urgency (20.9%), painful voiding (20.1%), difficulty (5.0%), and nocturnal incontinence (1.4%). Therefore, it seems prudent to offer such affected patients a choice of urinary alkalinizers prior to or concomitantly with an appropriate antibiotic therapy so as to provide symptomatic relief.[17,49]

In light of the above requirement, potassium citrate demonstrates superior efficacy in alkalizing urine.[50] This citrate preparation provides an alkali load and increases the urinary citrate, thereby maintaining a urinary pH

Box 1: Advantages of modified release nitrofurantoin

- Advantages of loading dose and maintenance
- Offers twice-daily dosage schedule with better gastrointestinal tolerability
- Recommended as a first-line therapy in lower UTI
- Better patient compliance
- Approved by United State FDA
- Indicated in uncomplicated lower UTI, recurrent cystitis related to coitus
- Safe for long-term usage (up to 12 months) in prophylaxis

Abbreviations: UTI - urinary tract infection; FDA - Food and Drug Administration

of 6.0–6.5.[51,52] This process makes the urine less acidic, which may serve to improve the condition of painful and burning micturition in patients with UTIs.[50,53] Besides alleviating symptoms, achievement of alkaline pH may also augment the natural defense mechanisms, including enhancement of phagocytosis, thereby destroying the infecting organisms, such as *E. coli* and *S. saprophyticus*.[54] Moreover, it may also assist in preventing later onset of urinary tract infection.[55,56]

Conclusion

Urinary tract infections are one of the most commonly encountered bacterial infections. Recurrent UTIs are most commonly caused by reinfection with the original bacterial isolate in young, otherwise healthy adult with no anatomic or functional abnormalities of the urinary tract. *E. coli* strains are responsible for majority of the infections. Long term prophylactic measures, including antimicrobial prophylaxis, decrease the continued high incidence of recurrent UTIs. In this context, nitrofurantoin is considered an effective therapeutic option for prophylaxis of recurrent lower UTIs as it is well tolerated, with the added advantage of minimal resistance and low propensity to induce development of drug resistance. It has been recommended as the first line therapy for the management of urinary tract infections by the Infectious Diseases Society of America guidelines. It is also important to treat the distressing symptoms of recurrent UTI, such as painful/burning micturition. Herein, potassium citrate therapy seems propitious, since it alkalinizes urine pH and thus relieves the distressing symptoms of UTIs.

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