Management of urinary tract infections: Role of nitrofurantoin amid antimicrobial resistance

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Introduction

Urinary tract infections (UTIs) are among the most prevalent infectious diseases globally, impacting 150 million people annually, resulting in significant morbidity and high medical expenses. While the symptoms of UTIs can differ based on the location of these infections, they adversely affect patients' personal and social relationships, leading to diminished quality of life.[1] In India, the prevalence of UTIs ranges from 21.8% to 31.3%.[2]

Bacteria are the predominant causative agents responsible for UTIs, although more rarely, other microorganisms like fungi and certain viruses have also been identified. Uropathogenic *E. coli* (UPEC) is the most frequent cause of uncomplicated and complicated UTIs. Most UTIs are caused by Gram-negative and Gram-positive bacteria that reside in the colon, like *E. coli*, *Enterococcus faecalis*, *Proteus mirabilis*, and *Klebsiella pneumoniae*. Other pathogens, including *Staphylococcus saprophyticus*, Group B *Streptococcus* (GBS), and *Pseudomonas aeruginosa*, can also be responsible.[1]

UTIs often begin when uropathogens from the gut colonize the urethra and later the bladder by specific adhesins. If the host's inflammatory response does not clear all bacteria, they proliferate, producing toxins and enzymes that facilitate their survival. Further colonization of the kidneys can lead to bacteremia if the pathogen crosses the kidney epithelial barrier. Bacterial proliferation can also result from biofilm protection, and if the infection remains untreated, it can lead to pyelonephritis and bacteremia. In many cases, the infection may not appear severe, particularly in the early stages, however, it can exacerbate significantly in the presence of complicating factors. These factors include biofilm formation, urinary stasis due to obstruction, and the use of catheters.[1]

Classification of UTIs

The classification of UTI is shown in Table 1.[1,2]

Table 1: Classification of UTI according to various conditions

Based on the site of the infection	Based on the presence of predisposing conditions for infection	Based on the nature of the event
• Urethritis (an infection of the urethra) • Ureteritis (inflammation of the ureter) • Cystitis (inflammation of the bladder) • Pyelonephritis (infection of the kidneys) • Urosepsis	• Uncomplicated UTI • Complicated UTI	• Primary infection • Recurrent infection

Management of UTIs

Antimicrobial therapy is the mainstay for treating any bacterial infection, including a UTI. Given the high prevalence of UTIs, particularly among women, it is crucial to use antibiotics in a controlled manner for effective treatment.[3] Oral nitrofurantoin, administered for 5 days, is one of the primary first-line agents for treating acute uncomplicated cystitis. Fosfomycin is a suitable alternative when nitrofurantoin cannot be used. It is crucial to avoid nitrofurantoin and fosfomycin when early pyelonephritis is suspected

due to poor penetration into the renal parenchyma. Trimethoprim-sulfamethoxazole (TMP/SMX) can be used empirically as a first-line treatment, except when local resistance rates to Enterobacteriales, including *E. coli*, exceed 20% or if the patient has taken it for an infection within the past three months.[4] Nitrofurantoin and fosfomycin both exhibit a favorable safety profile, achieve adequate concentration in urine, have a narrow spectrum of activity, and are widely used in various primary care settings.[5]

Oral β-lactams, including amoxicillin-clavulanate or cefpodoxime, can be effectively used as a second-line treatment for UTIs. These agents should be considered only if the first-line options are unsuitable due to allergies, availability issues, or resistance. Fluoroquinolones, such as ciprofloxacin, can be effective for treating UTIs but are usually not recommended as first-line options for uncomplicated cystitis owing to their side effects and to reduce the increasing rates of quinolone resistance. They are used for more severe infections like pyelonephritis.[4]

Combinations of ceftolozane/tazobactam or ceftazidime-avibactam are effective in treating UTIs caused by resistant strains of Enterobacteriales and *Pseudomonas aeruginosa*. Imipenem/cilastatin, cefiderocol, meropenem-vaborbactam, and plazomycin are the new class of antimicrobial agents used to treat UTI. These new agents can offer a viable treatment alternative for complicated infections resistant to carbapenems.[1]

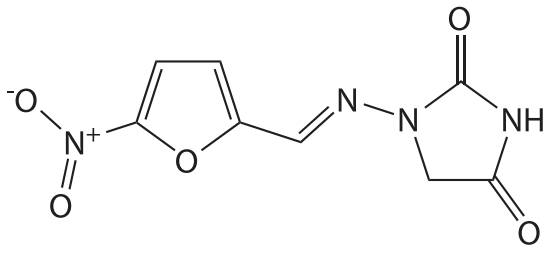
Antimicrobial resistance

UTIs are frequently treated with broad-spectrum antibiotics, with treatment initiated empirically without prior culture and sensitivity testing.[6] The widespread availability and use of more potent antibiotics purchased over the counter (OTC) is a common issue in India, similar to other low- and middle-income countries (LMICs). The use of OTC antibiotics like trimethoprim, sulfamethoxazole, fluoroquinolones, and particularly β-lactams to treat UTIs have long been suspected as a significant contributor to the development of antimicrobial resistance (AMR).[2] In a systematic review, resistance rates against trimethoprim/sulfamethoxazole, ciprofloxacin, and ceftriaxone ranged between 33% and 90%, with the highest prevalence observed in Bangladesh, India, Sri Lanka, and Indonesia.[7]

Role of nitrofurantoin in the treatment of UTIs

Nitrofurantoin (Figure 1), a broad-spectrum antibiotic available since 1953, is commonly used to treat UTIs due to its effectiveness against many drug-resistant uropathogens. It exhibits both bacteriostatic and bactericidal properties and is rapidly excreted in high concentrations by the kidneys.[8]

Figure 1: Chemical structure of nitrofurantoin



Nitrofurantoin inhibits bacterial growth at three different locations in the Kreb's cycle. Although about 25% of nitrofurantoin is excreted through the kidneys, a portion is also eliminated via the gastrointestinal tract. Unlike antibiotics with a high potential for resistance, nitrofurantoin does not induce resistance. Pharmacokinetically, the reabsorption of nitrofurantoin is pH-dependent. At the normal urinary pH of approximately 5.5, it is mainly excreted into the lower urinary tract, such as the bladder, making it beneficial for treating lower UTIs.[9]

In addition to its significant impact on uropathogens, nitrofurantoin also inhibits a broad spectrum of Gram-positive bacteria, including Staphylococcus and Enterococcus, as well as Gram-negative bacteria such as Klebsiella and Citrobacter. *E. coli*, the most commonly isolated bacterium in uncomplicated UTI cases, is particularly susceptible to nitrofurantoin compared to other Gram-negative bacteria. In contrast, Enterobacter, Klebsiella, Citrobacter, and Providencia are less responsive to nitrofurantoin, while Pseudomonas, Proteus, Acinetobacter, Morganella, and Serratia are resistant to it.[8]

Recommended dosage or therapeutic use[8]	• 50-100 mg every 6 hours (for the regular-release formulation) • 100 mg every 12 or 8 hours (for the slow-release formulation)
Recommended dosage for prophylaxis[8]	• 50-100 mg once daily

Efficacy of nitrofurantoin in the treatment of UTIs

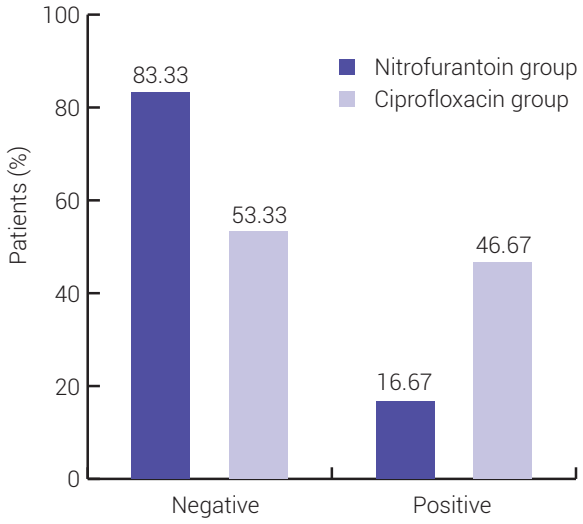
Twenty-seven trials involving 4,807 patients have investigated the use of nitrofurantoin for treating UTIs. The results indicated that nitrofurantoin is clinically and microbiologically effective, achieving clinical cure rates ranging from 79% to 92% and microbiological eradication rates of 80%-92%.[8]

A prospective, open, randomized, parallel-group, comparative study, involving 60 patients with acute/uncomplicated or recurrent UTI showed that nitrofurantoin is more effective than ciprofloxacin. Post-treatment urine samples showed the growth of microorganisms in 5 patients (16.67%) from the nitrofurantoin group and in 14 patients (46.67%) from the ciprofloxacin group, suggesting that nitrofurantoin is more effective (Figure 2).[10]

Another open-label/analyst-blinded, multicenter, randomized clinical trial including 513 nonpregnant women >18 years of age with uncomplicated UTI showed that a 5-day course of nitrofurantoin, compared to a single dose of fosfomycin, led to a significantly higher likelihood of achieving clinical and microbiologic resolution 28 days after completing treatment. By day 28, clinical resolution was achieved in 171 of 244 patients (70%) who received nitrofurantoin, compared to 139 out of 241 patients (58%) who received fosfomycin [difference of 12% (95% CI, 4%-21%); p = 0.004]. The microbiologic resolution was observed in 129 of 175 patients (74%) treated with nitrofurantoin, compared to 103 of 163 patients (63%) treated with fosfomycin [difference of 11% (95% CI, 1%-20%); p = 0.04].[11]

In another study, Gupta K and colleagues concluded that a 5-day regimen of nitrofurantoin is clinically and microbiologically similar to a 3-day regimen of TMP/SMX. Clinical cure was achieved in 79% and 84% of the TMP/SMX group and nitrofurantoin group, respectively.[12]

Figure 2: Urine culture results between the two groups post-treatment



Due to its effectiveness, affordability, and minimal impact on promoting antimicrobial resistance, clinicians should consider nitrofurantoin as a first-line option for treating uncomplicated UTIs.[13]

Nitrofurantoin is a viable alternative to TMP-SMX and fluoroquinolones for the empirical treatment of uncomplicated UTIs, particularly given the rising rates of antibiotic resistance among community uropathogens.[13]

Guideline recommendations on nitrofurantoin for treating UTIs

Guideline	Year	Recommendations
European Association of Urology Guidelines on Urological Infections	2024	Fosfomycin trometamol, pivmecillinam or nitrofurantoin are suggested as the first-line treatment for uncomplicated cystitis.[14]
Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline	2022	Clinicians should use first-line therapies, such as nitrofurantoin, TMP-SMX, or fosfomycin, based on the local antibiogram for treating women with symptomatic UTIs.[15]
Urinary tract infection (lower): antimicrobial prescribing; NICE guideline	2018	• Nitrofurantoin or trimethoprim is recommended as the first choice for non-pregnant women with lower UTI. • Nitrofurantoin (if not used as a first-choice), pivmecillinam (a type of penicillin), or fosfomycin is recommended as second-choice antibiotics if symptoms of a lower UTI do not improve after at least 48 hours of using a first-choice antibiotic, or if the first-choice antibiotics are not appropriate. • Nitrofurantoin is recommended as the first-choice antibiotic for pregnant women with lower UTI (not recommended in pregnancy at term). • Trimethoprim or nitrofurantoin at usual doses is recommended as first-choice antibiotics for men with a lower UTI (not recommended for men with suspected prostate involvement).[16]

Modified release nitrofurantoin

It is perceived that nitrofurantoin is associated with a higher incidence of nausea compared to other treatments for UTIs. A modified release (MR) formulation of nitrofurantoin has been developed to minimize the associated adverse effects. This MR system enables a more convenient twice-daily dosing regimen.[17]

In a study by Spencer RC and colleagues among 538 patients with uncomplicated UTI, the cure rates for *E. coli* infections were similar among the treatments: 81.5% for nitrofurantoin MR, 82.5% for co-trimoxazole, and 78.4% for trimethoprim. However, for non-*E. coli* pathogens, nitrofurantoin MR and co-trimoxazole showed equivalent cure rates of 86.7%, whereas it was higher than trimethoprim (72.0%). The three test drugs were well-tolerated. However, nitrofurantoin MR was associated with fewer drug-related adverse events (5.6%) than co-trimoxazole (8.8%) and trimethoprim (7.3%). Nitrofurantoin MR is a good alternative for first-line therapy due to its low resistance levels, favorable safety profile, and clinical effectiveness.[17]

The Scottish Intercollegiate Guidelines Network (SIGN) and NICE guidelines recommend a 3-day regimen of nitrofurantoin 100 mg MR twice daily or 50 mg taken four times daily as the first-line therapy for women with symptoms of uncomplicated UTIs who require antibiotics.[18]

Conclusion

Urinary tract infections (UTIs) are among the most common infectious diseases worldwide, affecting millions of individuals and leading to substantial morbidity and healthcare costs. The primary causative agents are uropathogenic bacteria such as *E. coli*, although other pathogens can also be involved. Effective management of UTIs is essential for improving patient quality of life and preventing complications.

Nitrofurantoin is the first-line treatment in the management of UTIs, due to its broad-spectrum activity and low resistance profile. Evidence from numerous studies has highlighted that nitrofurantoin is clinically and microbiologically effective. While traditional formulations have been associated with a higher incidence of nausea, the MR formulation of nitrofurantoin offers a more convenient dosing regimen and demonstrates fewer drug-related adverse effects compared to other standard treatments like co-trimoxazole and trimethoprim.

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