REVIEW ARTICLE 1

Nitrofurantoin: Potential Role in Managing Urinary Tract Infections

Reviewed by:

Dr. Alap Mehendale
MBBS, DNB (General Surgery), DNB (Urology)
Honorary Consultant Urologist and Renal Transplant Surgeon
at Jaslok Hospital, Mumbai.

Introduction

Urinary tract infections (UTIs) are among the commonest infections encountered globally impacting 150 million individuals every year.[1] UTIs can be uncomplicated or complicated, adversely affecting the patient's quality of life.[1] Women are more prone to develop UTIs compared to men on account of various factors (Figure 1).[2]

Figure 1. Factors that make women more prone to UTIs

Short urethra	No prostatic secretion
Ease of contamination from fecal flora	Pregnancy

Escherichia coli is the commonest organism known to cause UTI. Other pathogens include *Proteus mirabilis, Klebsiella* species, *Pseudomonas aeruginosa,* and *Enterobacter* species.[2] UTIs are less commonly caused by fungi and viruses.[1]

A retrospective analysis of urine culture results at a tertiary care hospital in Mumbai, India, noted a UTI prevalence of 33.54%. The prevalence was higher among women. The most common isolate was *E. coli,* followed by *Klebsiella pneumoniae*. Resistance was noted to fluoroquinolones, amoxicillin and third-generation cephalosporins.[2]

As mentioned earlier, UTIs can be uncomplicated or complicated and can be primary or recurrent.[1]

Uncomplicated UTI

Healthy individuals are affected when there is no structural or neurological abnormality of the urinary tract

Complicated UTI

Urinary tract abnormalities are present which heighten the vulnerability to infection

Recurrent UTI

Recurrent UTI is described as ≥3 uncomplicated UTIs within a sapn of 12 months or ≥2 episodes of infection within a 6-month duration.[1]

Management of UTIs

Asymptomatic bacteriuria does not need to be treated. However, it may require treatment in immunosuppressed individuals, pregnant women, those who underwent a transplantation, or those who have undergone a urologic surgery.[3]

In case of uncomplicated UTI, first-line treatment includes nitrofurantoin, fosfomycin, trimethoprim/sulfamethoxazole (TMP/SMX), and pivmecillinam.[1] TMP/SMX should be considered only when the local *E. coli* resistance is not over 20%. Second-line treatment includes cephalosporins, fluoroquinolones, and β-lactams.[1] First-generation cephalosporins can be used as mini-dose therapy (3 days). Fluoroquinolones may not be the choice for uncomplicated UTIs but are preferred in cases of pyelonephritis and prostatitis.[3]

For uncomplicated pyelonephritis, first-line treatment includes oral fluoroquinolones. Other agents include TMP/SMX and β-lactams. Intravenous (IV) antibiotic therapy is needed in case of complicated obstructive pyelonephritis.[1]

For complicated UTI, initial therapy includes IV amoxicillin+aminoglycoside, second-generation cephalosporin+aminoglycoside, or third-generation cephalosporin+aminoglycoside. For complicated UTI due to multidrug resistant organisms, ceftolozane/tazobactam, imipenem/cilastatin, or ceftazidime/avibactam can be considered.[1]

Role of Nitrofurantoin in Managing UTIs

Nitrofurantoin is a first-line agent in the management of uncomplicated UTIs.[1] In low concentrations, the drug acts as a bacteriostatic and in higher concentrations, it is bactericidal.[4]

Various guidelines recommend nitrofurantoin as an antimicrobial treatment for urological infection. The European Association of Urology recommends nitrofurantoin as a first-line treatment option for uncomplicated cystitis in females. The duration of treatment is 5 days.[5] Nitrofurantoin can be considered for cystitis in pregnant women, except for those with glucose-6-phosphate dehydrogenase deficiency and at the end of pregnancy. It can also be considered for recurrent UTIs.[5]

The American Urological Association (AUA)/Canadian Urological Association (CUA)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) guideline also recommends nitrofurantoin as a first-line treatment option for symptomatic UTIs among women, based on the local antibiogram.[6] The agent is not associated with any collateral damage and the resistance is low.[6] It can be used for continuous prophylaxis as well as for prophylaxis of post-coital UTI.[6]

Additionally, the guidelines for antimicrobial use by the Indian Council of Medical Research also advocate nitrofurantoin as the choice of therapy for acute cystitis for empiric treatment. It can also be used in children with cystitis. In children with vesicoureteric reflux, nitrofurantoin or co-trimoxazole is the choice of treatment for those older than 3 months. The dosage is 100 mg twice daily for 5 days in adults while in children, it is 1.25-1.75 mg/kg every 6 hours.[7]

Furthermore, in catheter-associated UTI (CA-UTI), when the patient does not present with severe illness or there are no upper UTI symptoms, nitrofurantoin can be considered.[7]

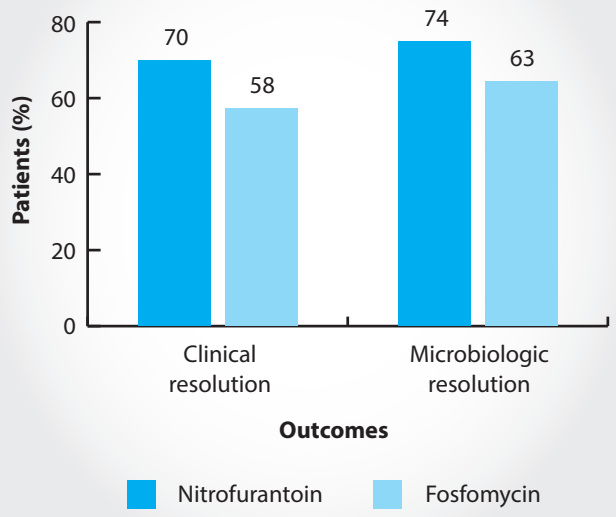
According to the Infectious Diseases Society of America guidelines also, nitrofurantoin 100 mg twice a day for 5 days is a suitable treatment option for acute uncomplicated cystitis owing to low resistance and minimal tendency for collateral damage. It has effectiveness similar to 3-day TMP/SMX therapy.[8]

The American College of Obstetricians and Gynecologists' consensus on UTIs in pregnant women advocates nitrofurantoin 100 mg 12-hourly for 5 to 7 days as a reasonable choice in the first trimester. Nitrofurantoin can remain the first-line treatment for UTIs during the second and third trimesters. Additionally, after pyelonephritis treatment, if suppression therapy is started, nitrofurantoin 100 mg daily can be given for the rest of the pregnancy and till 4 to 6 weeks postpartum. For recurrent UTI as well, suppressive treatment can include nitrofurantoin 100 mg every day.[9]

Nitrofurantoin in uncomplicated UTI

Nitrofurantoin has been reported to be effective in uncomplicated UTI. A study compared the efficacy of nitrofurantoin and fosfomycin in women having uncomplicated cystitis. Seventy percent of the patients who received nitrofurantoin attained clinical resolution through day 28 compared to 58% of the patients who received fosfomycin. Microbiologic resolution was evident in 74% of the patients receiving nitrofurantoin compared to 63% of the patients receiving fosfomycin (Figure 2).[10]

Figure 2. Patients with clinical and microbiologic resolution with nitrofurantoin and fosfomycin



A study evaluated the efficacy of nitrofurantoin and TMP/SMX in women with acute uncomplicated cystitis. Clinical cure rate was 84% in the nitrofurantoin group compared to 79% in the TMP/SMX group. 5-day nitrofurantoin regimen has been noted to be clinically and microbiologically comparable to 3-day TMP/SMX regimen.[11]

Nitrofurantoin to manage UTI in children

A study evaluated the clinical and microbiological efficacy of oral nitrofurantoin in lower UTI due to extended-spectrum β-lactamase (ESBL)-producing *E. coli* among children. Overall, 98% of the patients had bacteriological response and there were no significant side effects. Nitrofurantoin could thus be a potential option in children to manage lower UTI due to ESBL-producing *E. coli*.[12]

In a study comparing nitrofurantoin and trimethoprim prophylaxis to prevent recurrent UTIs in children, nitrofurantoin was found to be the most effective prophylactic medication for those with abnormal urography and/or reflux, as determined through an actuarial percentage recurrence-free analysis.[13]

Nitrofurantoin in recurrent UTI

Long-term use of nitrofurantoin may have a favorable effect in preventing UTIs in spinal cord injury (SCI) patients with recurrent UTIs. A study assessed the effect of long-term nitrofurantoin for the prophylaxis of UTIs in veterans with SCI. Cases received nitrofurantoin while controls did not. UTIs were less common among cases after differences in baseline demographic characteristics were adjusted.[14]

A systematic review and meta-analysis found nitrofurantoin to have comparable efficacy to other prophylactic treatments for recurrent UTIs; however, the risk of adverse events was higher and must be balanced with the benefits.[15] Severe adverse effects seem to be rare.[16] In a study evaluating the prophylactic effect of nitrofurantoin and TMP-SMX in recurrent UTI among children, nitrofurantoin was found to be more effective for prevention of recurrent UTI, with recurrence rates of 36.2% and 63.8% in the nitrofurantoin and TMP-SMX groups. Additionally, nitrofurantoin appeared to be associated with lesser development of resistant bacteria compared to TMP-SMX.[17]

Nitrofurantoin and cranberry products may help reduce the occurrence of episodes of symptomatic UTI in children with a history of recurrent UTIs.[18]

Modified-release Nitrofurantoin

Modified-release (MR) formulation of nitrofurantoin should be favored over conventional ones as MR nitrofurantoin use is associated with immediate release of a part of the drug, quickly accumulating in the urine for rapid action within the first hour. Rest of the drug is gradually released maintaining sufficient concentration in the urine throughout the day. MR formulations sustain urinary concentration for up to 12 hours and are associated with improved gastrointestinal (GI) tolerability. They tend to reduce the dosing frequency to twice daily and increase compliance.[19]

Conclusion

UTIs affect millions of people globally and have an adverse impact on a patient's quality of life. Considering the growing antimicrobial resistance of pathogens to commonly used antibiotics, it is important to choose wisely.

Nitrofurantoin is a bacteriostatic and bactericidal agent that has been recommended as first-line therapy in uncomplicated UTIs. The drug also seems to have a role in prophylactic treatment of recurrent UTIs and in UTIs in children.

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