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# Efficacy of Nitrofurantoin in Treating Urinary Tract Infections

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**Abstract:** *Urinary tract infections are often caused by bacteria resistant to antibiotics which have evolved to be a major health issue in recent years. Often, urinary tract infections are very hard to treat and if not appropriately treated in time, may result in serious consequences, particularly, when it spreads to kidneys ultimately resulting in an increase in morbidity and mortality. Nitrofurantoin, a first line agent and has bactericidal action, frequently used to treat uncomplicated urinary tract infection. The literature was searched with published sources from Medline, PubMed and Embase search engines. Published articles were searched, of which 81 articles were eligible to be included for this systematic review. Nitrofurantoin is reduced by the action of bacterial flavoproteins to reactive intermediate compounds that non-specifically inactivate ribosomal proteins resulting in inhibition of protein synthesis. Various mechanisms seem to be responsible for the reduced capability of microorganism to acquire resistance in a faster manner. Nitrofurantoin exhibits high quality success against most bacteria anticipated in urinary tract infection. Nitrofurantoin has been recommended for prophylaxis in the treatment of reinfection in case of recurrent uncomplicated urinary tract infections in many western countries. Nitrofurantoin is one of the treatment options for urinary tract infection due to extended spectrum beta lactamase producing Escherichia coli. In pregnant women with urinary tract infection, nitrofurantoin can be appropriate treatment. Also, nitrofurantoin associated reactions have been reported in many studies. This review updates the clinical use of nitrofurantoin, including new facts about the role of nitrofurantoin in the therapy of community acquired urinary tract infection, adverse outcomes, complications, interactions and antibiotic resistance mechanism against different uropathogens.*

*Nitrofurantoin is an old antibiotic and an important first-line oral antibiotic for the treatment of uncomplicated urinary tract infections. However despite its long term use for over 60 years, little information is available with respect to its dose justification and this may be the reason of highly variable recommended doses and dosing schedules. Furthermore, nitrofurantoin is not a uniform product -crystal sizes of nitrofurantoin, and therefore pharmacokinetic properties, differ significantly by product. Moreover, pharmacokinetic profiling of some products is even lacking, or difficult to interpret because of its unstable chemical properties. Pharmacokinetic and pharmacodynamic data is now slowly becoming available. This review provides an overview of nitrofurantoins antibacterial, pharmacokinetic and pharmacodynamic properties. This shows that a clear rationale of current dosing regimens is scanty.*

**Keywords:** pharmacokinetics; pharmacodynamics; urinary tract infections; antibiotic, Pain relief

## I. INTRODUCTION

Nitrofurantoin is an old antibiotic used for the treatment of uncomplicated urinary tract infections (UTI) for decades (1–3). Registered in 1953, its popularity has been increasing recently mainly because of the emergence of multi-drug resistance (including β-lactam and quinolone resistance) amongst gram-negative micro-organisms (2, 4). Resistance rates for nitrofurantoin are still low despite its extensive use (5, 6). Its spectrum of activity includes (vancomycin-

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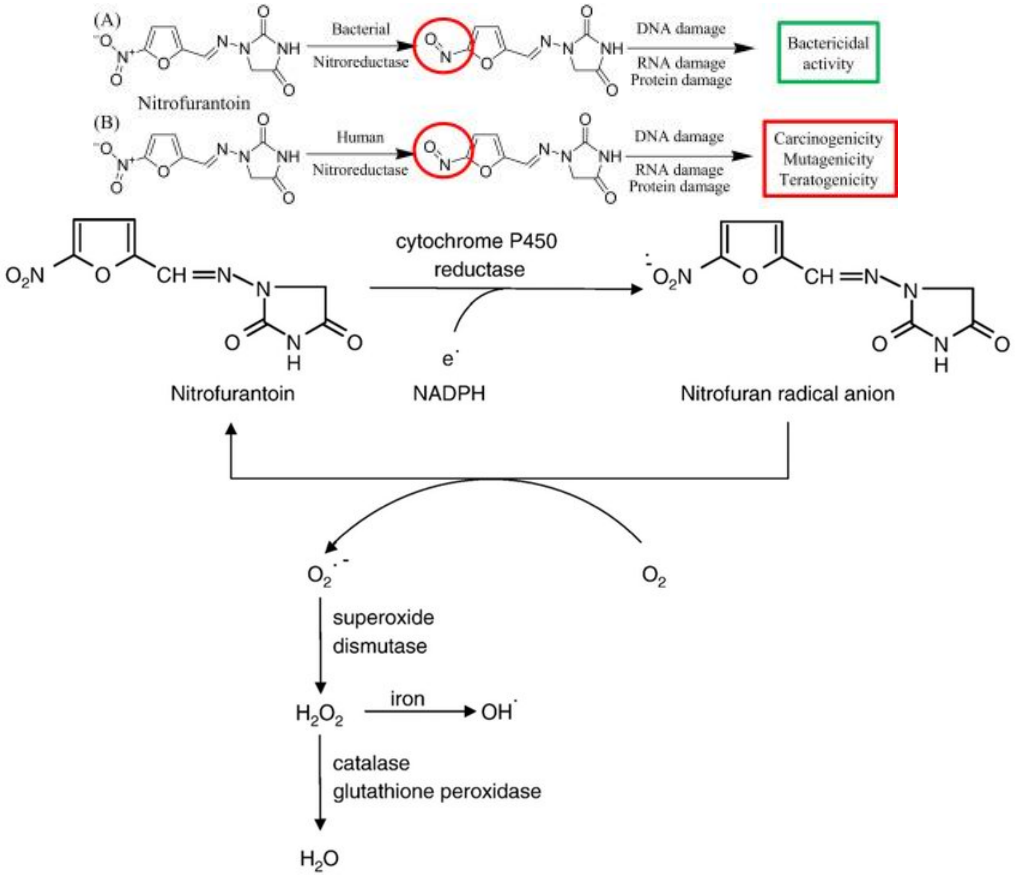
resistant) enterococci and Enterobacterales -including extended beta-lactamase (ESBL) producers, but with the exception of some Klebsiella strains and Proteae (e.g. Proteus, Morganella, and Providencia spp) which are intrinsically resistant (7–10). Positive clinical outcomes of percentage up to 90% for uncomplicated UTIs are reported for nitrofurantoin (6, 11, 12). The most recent international guidelines therefore lists nitrofurantoin as a first line treatment option for uncomplicated UTIs in many countries worldwide (2). Nitrofurantoin is the only member of the nitrofuran family currently in use in human medicine and is available as an oral formulation only. There are various nitrofurantoin products on the market of which the 50 mg and the 100 mg capsules are the most commonly prescribed products in clinical practice. Other formulations available are the slow-release capsule and the oral suspension. Despite its long time availability pharmacokinetic and pharmacodynamic (PK/PD) data are scarce, and the relationship between exposure and response is not clear, although it is well know that these data are crucial in treatment optimization and prevention of emergence of resistance (13, 14). The aim of this paper is therefore to provide an overview of existing clinical and in vitro PK/PD data. This may serve as a basis to provide guidance to assess missing PK/PD related information.

**ADVANTAGES**

Nitrofurantoin is an antibiotic medication is used for the treatment of uncompleted lower urinary tract infection . It is effective against most gram positive and gram negative organisms. Nitrofurantoin primary use has remained in treating and prophylaxis of urinary tract infection.It works by killing bacteria that cause infection.




SI

**SIDE EFFECT :-**

1) Feeling sick (nausea)
2) Vomiting

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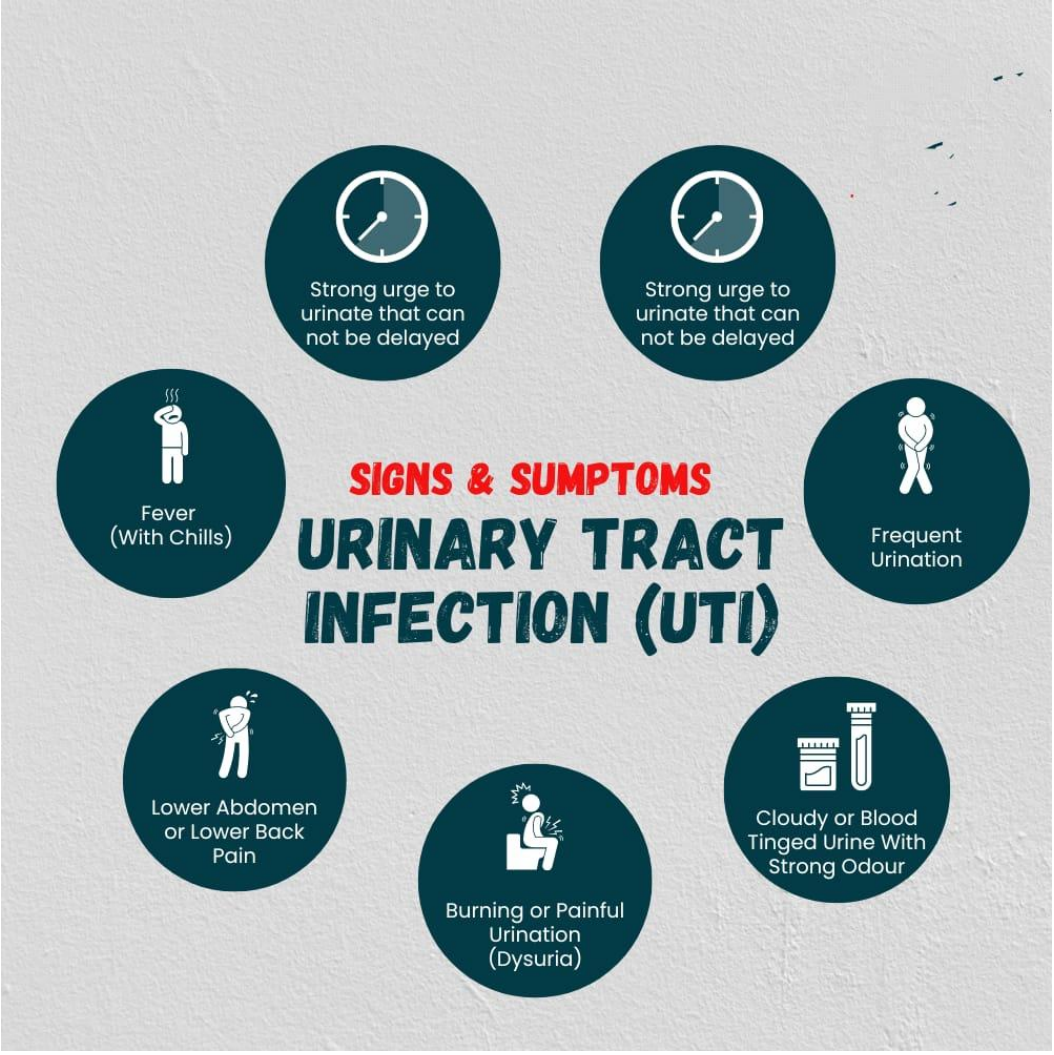
3) Loss of appetite
4) Diziness or feeling sleepy

**Signs and symptoms**




## II. MATERIAL AND METHODS

Study design, subjects, drug administration and sample collection Urine samples to determine the UIT and UBT were obtained in two previous studies evaluating the PK properties of the both fosfomycin and nitrofurantoin (7, 8). Briefly, the fosfomycin urinary PK study was a single-center study to examine the urinary PK following a single, oral 3 gram dose of fosfomycin trometamol (Monuril, Zambon Nederland B.V., Amersfoort, the Netherlands) in 40 healthy, female volunteers (7). Fosfomycin was administered under supervision of one of the researchers. Urine samples were collected in a home setting over 48 hours with every void and two times daily from 48 hours until 7 days after administration. For the present study, we used only the samples collected in the first 48 hours. There were no dietary restrictions prior to or after drug administration. Samples were kept in home freezers until handed in to investigators. The nitrofurantoin PK study was a single-center study in which macrocrystalline nitrofurontoin was administered either 50 mg q6 hours (Fuarantine MC, Mercury Pharma Ltd, Croydon UK) or 100 mg q8 hours (Furadantine® retard, Mercury Pharma Ltd, Croydon UK) in a crossover design to 12 healthy, female volunteers (8). The drug was administered with food and

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administration began in a home setting 24 hours prior to sample collection to achieve steady state. The last dose was administered in the hospital at the start of the 8-hour visit, during which urine samples were collected for 6 hours or 8 hours, depending on the assigned dosing interval. Volunteers were instructed to protect the nitrofurantoin samples from daylight using aluminum foil to avoid photodegradation of the drug.

Determination of UITs and UBTs All urine samples were filtered before analysis by centrifugation (10 minutes at 13.000 rpm) using Amicon Ultra-0.5 centrifugal filter units with a 10 kDa cutoff Ultracel-10 membrane (UFC5010BK; Merck, Amsterdam, the Netherlands). The large volumes of antibiotic-free urine were filtered over 0.2 µm bottle-top vacuum filters (CLS430756; 4 Erasmus Medical Center Rotterdam Corning, Taufkirchen, Germany). UITs and UBTs were determined by microdilution. Urine samples underwent a serial two-fold dilution series in antibiotic-free urine from healthy volunteers such that the first well of the microtiter plate contained a 2-times diluted sample. The final bacterial inoculum within the microtiter tray was approximately 2.5 x 105 CFU/ml. Inoculated plates were incubated for 18 ± 2 hours at 35 ± 2o C. After which every well was checked visually for growth. The UIT represents the bacteriostatic activity and was defined as the highest dilution that inhibited visible growth. The UBT represents the bactericidal activity and was defined by the absence of bacterial growth following a subculture from the microtiter tray onto an antibiotic-free Tryptic Soy agar plate supplemented with 5% sheep blood (TSB, 254087, Becton Dickinson, Franklin Lakes, NJ, USA). The limit of detection was 50 cfu/ml. TSB plates were incubated for 18 ± 2 hours at 35 ± 2o C. The UBT was defined as the highest dilution of the sample that still exhibited bactericidal activity. Comparable UIT and UBT reflect antibiotic bactericidal activity, while a UIT exceeding the UBT reflects bacteriostatic activity. UITs and UBTs are presented as reciprocal values of the titers and could therefore range from <2 (no antibacterial activity observed) to 1024, with higher titers indicating greater antibacterial activity. Determination of fosfomycin-resistant subpopulation To determine the presence of Fosfomycin low-level resistant (LLR) or high-level resistant (HLR) subpopulations, isolates were cultured overnight in both Muller-Hinton Table 1. MICs of fosfomycin and nitrofurantoin. The MIC represents the modal value based on the results of agar dilution (Fosfomycin) or micro dilution (nitrofurantoin) performed in triplicate. Test strain Source MIC Fosfomycin (mg/liter)a MIC Nitrofurantoin (mg/liter) E. coli ATCC 25922 Laboratory strain 1 16 51b Blood 2 32 03 b Urine 0.25 16 1231 Urine 16 512 4807 Rectal swab 32 16 K. pneumoniae 58 b Urine 8 64 20 b Rectal swab 32 256 31865 Blood 2 128 55 Sputum 4 256 a The MIC represents the modal value based on the results of agar dilution (Fosfomycin) or microdilution . A prospective cross-sectional study was conducted in the Department of Pediatrics, Ankara University School of Medicine, between January 2003 and January 2004. Urine was collected from children admitted to the Department of Pediatrics in whom UTI was considered a possibility on clinical grounds. Cases showing pyuria and significant bacterial growth on culture were included in the study. All urine samples collected by midstream clean-catch, catheterization or urine bags were obtained. These samples were processed on blood agar and MacConkey medium with a standard loop and were incubated at 37 ◦C overnight. Significant growth was evaluated as ≥105 colony-forming units (CFU)/mL of midstream urine and bag urine samples, and ≥102 CFU/mL of a catheter specimen. Identification of Gram-negative bacteria was performed by standard biochemical methods and confirmed with ID 32 (Mini API; bioMerieux, Lyon, France) ´ [5]. Antimicrobial susceptibility testing was performed by the disk diffusion method on cultures with significant bacteriuria using a panel of antimicrobial agents depending on the causative organism. Interpretations followed the National Committee for Clinical Laboratory Standards criteria [6]. Extended-spectrum -lactamase (ESBL) activity was detected by the double-disk synergy method using amoxicillin/clavulanic acid and ceftriaxone disks. ESBL-producing strains were confirmed with the ATB G-5 (bioMerieux) ´ [5]. A clinical diagnosis of upper UTI was made on the basis of the presence of systemic symptoms such as fever (≥38.5 ◦C), vomiting, flank/back pain and elevated acute phase reactants such as C-reactive protein (>2 mg/dL) and erythrocyte sedimentation rate (>20 mm/h). Children with clinical upper UTI were hospitalized and were treated with parenteral antibiotics for 10 days. Renal cortical scintigraphy was performed for the detection of renal inflammation within 6 days of the onset of symptoms[7,8]. Children with lower UTI were managed on an outpatient basis [8]. The following information was obtained from the patients' medical histories: (1) voiding dysfunction; (2) first or recurrent UTI; (3) antibiotic prophylaxis; and (4) urinary anomaly causing vesicoureteral reflux (VUR). Patients with genitourinary abnormalities, except VUR, were excluded. In addition, to analyze resistance to antibiotics in different ages, subjects were divided into three age groups: Group I, ≤12 months; Group II, 13–60 months; and Group III, >60 months. During the period 1 January/31 December 2001, 184 fresh

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midstream urine samples were collected from arbitrarily selected women between 15 and 65 years of age with symptoms of acute uncomplicated UTI who attended 17 general practice clinics in the County of Telemark, Norway. Dipstick urinalysis for nitrite and leukocyte esterase was performed at point of care using commercially available dipsticks. Results were registered as positive or negative. A sample of 20 ml of urine was sent by post or local courier for culture to the laboratory in sterile containers with 1.6% boric acid added. Trans port time was 1/24 hours. Women in whom empiric antibacterial treatment was started according to the GP's standard procedures were included in the study. The last three months, diabetes mellitus, previous upper urinary tract infection, other urinary tract pathologies, pregnancy, or antibiotic use during the previous two months.

## III. DISCUSSION

While Fosfomycin exhibited bactericidal activity for at least 48 hours against E. coli, no antibacterial activity was detected in the majority of K. pneumoniae samples. In contrast to Fosfomycin, nitrofurantoin showed low antibacterial activity in both species regardless of the administered dose, though only one dose interval was examined among the many intervals intended with a course of nitrofurantoin.

UTI in pregnancy is associated with significant morbidity for both mother and baby.

Early detection and treatment with antibiotics will significantly reduce complication associated with UTI.

Increasing antibiotic resistance among urinary tract isolates is mostly against ampicillin in many countries. The resistance rates to ampicillin were found to be 45%, 50% and 100% in children from Canada, Europe and Africa, respectively [1–4,9]. In our study, the frequency of resistance to ampicillin (74.2%) was also higher than the other antibiotics. The use of ampicillin as a single agent for empirical treatment of a suspected UTI would not cover the majority of urinary pathogens in our region. However, the combination of ampicillin and an amino glycoside is still used as an option in empirical treatment for upper UTI in Turkey. A recent study from Germany confirmed that initial empirical intravenous therapy of UTIs with this combination would be appropriate: resistance rates of causative agents to ampicillin and netilmicin were 51% and 7%, respectively [3]. In another study from Australia, gentamycin has been proposed as monotherapy for the effective and safe management of UTI requiring parenteral treatment in children aged 1 month to 12 years[10]. However, the resistance rate to gentamicin was 25% in children under 12 months in our study. In our population, amikacin is a more suitable aminoglycoside for treatment of children with UTI in the first year of life, whereas gentamicin may be adequate in children aged >1 year (9% resistance rate). Therapeutic Uses of Nitrofurantoin Urinary Tract Infection- Nitrofurantoin is advocated as first line therapy for uncomplicated UTIs in women. Nitrofurantoin is especially used to treat UTIs caused by Gram-negative bacteria, particularly Escherichia coli. 22 Nitrofurantoin is being advised for adults and children in the therapy of acute symptomatic UTIs. Also, prescribed for the treatment of recurrent UTIs and for the prophylaxis of recurrent UTIs.5 Nitrofurantoin is beneficial for treating UTIs in older women with low glomerular filtration rates.23 Since nitrofurantoin reaches therapeutically active concentrations only in lower urinary tract, hence it is neither recommended for upper UTI treatment nor for men with UTI and concomitant prostatitis.24 Acute Uncomplicated UTI- Acute uncomplicated cystitis is one of the most common health problems in the society for which young women seek medical attention. These inflammatory diseases are most commonly caused by Escherichia coli, can be treated by number of oral antibiotics, although increasing resistance are reported to some of the commonly used antimicrobial agents, particularly trimethoprim-sulphamethoxazole (TMP-SMX) combination. In women having risk factors for infection with resistant bacteria, or in the situation of a high prevalence of TMP-SMX resistant bacteria, a fluoroquinolone or nitrofurantoin should be considered for empirical treatment. Use of nitrofurantoin does not have chances of cross-resistance. Beta-lactams and fosfomycin may be suggested as second line agents for empirical treatment of cystitis.25 Acute Cystitis- Cystitis can be defined as the inflammatory condition of the urinary bladder with various and often unknown etiology. The most familiar pathogen in uncomplicated and complicated cystitis is uropathies Escherichia coli strain, followed by S saprophyticus, enterococci, coagulase-negative staphylococci, and other species of Enterobacteriaceae. 26,27 Cystitis can be clinically reported as a syndrome of dysuria, urgency, frequency, and lower abdominal pain. While cystitis is usually occurred by bacterial infection, it can also be induced by non-infectious conditions such as carcinoma in situ, bladder cancer, and bladder stone or it can even emerge from unknown origin as in interstitial cystitis.26 Uncomplicated cystitis can be reported as an infection in women with a structurally and functionally normal urinary

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bladder. However, complicated cystitis is related to structurally or functionally abnormal urinary bladder, where the host cell immunity is compromised and microorganisms develop antimicrobial resistance.28,29 Classical symptoms of uncomplicated cystitis are acute, and include dysuria, urge, and increased urinary frequency. These symptoms give rise to a 95% post symptom probability for uncomplicated cystitis.30 With reported research outcome data, following treatment options are available- 1. No treatment: Symptoms self-limited,31 increased fluid intake by the patient may be helpful for the recognition of the condition, and complications are rare. 2. Wait-and watch the prescription: This plan of action has resulted in decreased use of antibiotics for other infections encountered in general practice.32 3. NSAIDs used for symptom relief: Ibuprofen has shown similar efficacy to ciprofloxacin in symptomatic relief.33 4. Three days' treatment with a suitable antimicrobial agent is recommended.34 Three days' treatment of uncomplicated cystitis has the same effect as extended course of therapy, but fewer adverse effects have been reported associated with three day's therapy.33 Nitrofurantoin should be considered because of low resistance report. Trimethoprim is as effective as cotrimoxazole in uncomplicated cystitis with fewer adverse effects. Pimeclones also show favorable resistance levels. Quinolones should be restrained in case of more life-threatening infections and have no role in the empiric treatment of uncomplicated cystitis. The most successful therapy for an uncomplicated cystitis is a three-day course with TMP-SMX.35 There was no difference in symptom improvement between 3 days and 5-10 days of antibiotic use in women with uncomplicated cystitis, however the best therapeutic outcome from the microbiological aspect were reported with 5-10 days therapy.34,36 Pyelonephritis- In patients of uncomplicated pyelonephritis, fluoroquinolones are better to TMP-SMX for empirical therapy because of presence of TMP-SMX resistance against uropathogens causing pyelonephritis. However, TMP-SMX is a suitable option for patients with mild to moderate uncomplicated pyelonephritis, if the uropathogen is known to be susceptible to this agent. It is rational to use 7-10 days oral fluoroquinolone for outpatient management of mild to moderate pyelonephritis in the surroundings of a susceptible causative pathogen. The majority of women with acute uncomplicated pyelonephritis are managed carefully and effectively in outpatient setting.25 The frequency of acute pyelonephritis in majority of reported studies ranges from 0.5% to 2% of all pregnancies.37 The customary antibiotics used for the treatment of acute pyelonephritis include nitrofurantoin, cefazolin, cephalexin, ceftriaxone, and gentamicin.38 Nitrofurantoin or amoxicillinclavulanic acid are effective in terms of bacterial sensitivity, but nitrofurantoin should be avoided in patients with pyelonephritis, the reason being poor serum and tissue levels.

## IV. CONCLUSION

We found strong bactericidal activity of Fosfomycin against E. coli over at least 48 hours after administration and moderate bactericidal activity against K. pneumoniae over 18 hours. High-level resistant subpopulations were found in all K. pneumoniae strains and in one of the E. coli strains, findings that further support the likelihood of intrinsic resistance of K. pneumoniae against Fosfomycin, and highlight that MIC measurements might not be the best measure for predicting ex-vivo activity of Fosfomycin. Titers 14 Erasmus Medical Center Rotterdam of nitrofurantoin were comparable for both E. coli and K. pneumoniae, demonstrating moderate bactericidal activity in the first 2 hours after dosing. In the majority of subsequent samples, however, no antibacterial activity was detected, regardless of the administered dose. This finding is in contrast to nitrofurantoin's well-observed clinical effects over multiple dosing intervals. Our findings reveal a discrepancy between nitrofurantoin's measurable ex vivo activity in a single dosing interval time period and its clinical effectiveness. For Fosfomycin, our findings suggest that the current single-dose approach to Fosfomycin administration in UTIs caused by E. coli without HLR may be sufficient, but confirm the doubts of the use of Fosfomycin in general in UTIs caused by K. pneumonia.

Nitrofurantoin achieves therapeutic concentrations only in lower urinary tract. This limits its use to the treatment of lower UTI. Nitrofurantoin is highly active against Escherichia coli and S saprophyticus isolates. The toxicity of short course of therapy with nitrofurantoin is mild and predominantly gastrointestinal. Nitrofurantoin had similar effectiveness when compared to other antibiotics indicated for the treatment of UTI patients, but has a greater risk of adverse events than other prophylactic treatment regimens. However, the disclosure of antibiotic resistance and the decrease in recently developed antibiotics have led to an increasing interest in the treatment and prophylaxis of bacterial UTI with nitrofurantoin.

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This is the first UHPLC-DAD method suitable for the quantification of nitrofurantoin concentrations in plasma and urine with a small sample volume and a short analysis time. The method was found to be selective ad sensitive with low LLOQ concentrations. These properties ensure that the method is highly suitable for use during the daily routine for analyzing patients' samples in the context of clinical care and research where it can serve as a base for therapy evaluation and optimization. The applicability of the method was demonstrated during its use in a clinical study.

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