Re-Optimizing Nitrofurantoin Use in the Management of Uncomplicated and Complicated UTIs in Patients with CKD and Renal Transplants

Reviewed by:

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Introduction

Urinary Tract Infections (UTIs) are a highly significant and complex clinical challenge in patients with CKD and, most critically, in recipients of a renal transplant.[1,2] These infections encompass a range of microbial invasions affecting various parts of the urinary system, including the bladder, urethra, and, more critically, the transplanted kidney itself. UTIs hold unique clinical significance in renal transplantation due to the complex interplay of immunosuppressive regimens, altered urinary tract anatomy, and the lifelong implications for graft function and patient well-being. UTIs in renal transplant recipients are distinctive in their potential to disrupt the delicate balance between immune suppression and graft protection. Unlike in the general population, where UTIs are often self-limiting, the consequences can be dire in this vulnerable patient group. The significance lies in potential complications ranging from acute graft dysfunction to pyelonephritis, sepsis, and graft loss. Understanding the unique challenges UTIs present in renal transplant recipients is paramount for the healthcare community.[1]

The epidemiology of UTIs in renal transplant recipients is particularly notable. These infections are prevalent and often recurrent, contributing to a considerable burden of 4%-80% on healthcare resources.[2] In the United States, complicated UTIs result in over 626,000 hospital admissions annually, accounting for about 1.8% of all hospitalizations, with 80% of these cases being non-catheter-related. The incidence of UTIs increases in cohorts with multiple risk factors, including female gender, advanced age, diabetes, obesity, long-term catheter use, and frequent intercourse (though UTI is not classified as a sexually transmitted infection). The estimated incidence of simple UTIs in nonpregnant, immunocompetent females is as high as 0.7 infections per person annually. Half of all females will experience at least one UTI in their lifetime. The incidence of complicated UTI is linked to specific risk factors. For instance, the daily risk of developing bacteriuria with an indwelling bladder catheter is 10%, with up to a 25% risk of that bacteriuria progressing to a UTI.[3] Various factors, including post-transplant time frame, patient demographics, and comorbidities, influence the prevalence. Accurate data on the incidence and prevalence of UTIs in this population is essential for clinicians, researchers, and policymakers, as they guide the allocation of resources and the development of preventive strategies.[1]

UTI is the most common infectious complication in Kidney Transplant Recipients (KTR), with a cumulative incidence of up to 53.7% during the first year and prevalence rates ranging from 7.3% to 75%. Lack of uniformity in diagnostic criteria, variability in immunosuppression, and differences in the use of antimicrobial prophylaxis account for the variation in prevalence. Known risk factors include older age, female sex, obesity, diabetes, urinary tract abnormalities, systemic diseases, deceased kidney donor, time on dialysis, use of a urethral stent, allograft dysfunction, hepatitis C infection, Cytomegalovirus (CMV) infection, over-immunosuppression, and CKD itself, which leads to functional alterations in the urinary tract (such as reduced antibacterial properties of urine, loss of the urothelial protective mucosa, and immunological changes associated with uremia). Gram-negative microorganisms account for more than 70% of UTIs, with *Escherichia coli* (*E. coli*) being the most common pathogen (30–80%).[4]

Signs and symptoms of UTI vary by age, gender, and the presence of a catheter. In young women, symptoms typically include a frequent and intense urge to urinate and a painful, burning sensation in the bladder or urethra during urination. However, the quantity of urine may be

very small. In older women and men, symptoms include tiredness, lethargy, and weakness, accompanied by muscle aches and abdominal pain. The color of the urine may vary from cloudy or dark, to bloody and may a foul odor. In patients with a catheter, fever may be the only symptom that cannot be attributed to another cause. Usually, with the involvement of the bladder only, UTIs do not cause fever. Fever may be the primary sign indicating infection that has reached the kidneys or penetrated the prostate. Other symptoms of a kidney infection may include pain in the back or side below the ribs, nausea, and vomiting.[5]

Recurrent UTIs in transplant recipients can be vexing. They may result from various factors, including unresolved prior infections, anatomical abnormalities in the urinary tract, or complications arising from urological procedures post-transplant. These recurrent infections pose a significant clinical concern as they can negatively impact the patient's quality of life and potentially lead to complications such as graft dysfunction.[1]

The unique pathophysiological context of the renal transplant recipient amplifies the risks of UTI. To prevent allograft rejection, patients must undergo a regimen of potent immunosuppressive medications, a state of aggressive immune suppression that is most pronounced during the first year post-transplant (particularly within the first 3–6 months). This state intentionally weakens the body's ability to combat pathogens, making the patient highly susceptible to opportunistic and routine bacterial infections. As a result, any symptomatic UTI in a transplant recipient is considered "complicated", irrespective of its anatomical location (upper or lower urinary tract).[2,6]

This classification is crucial because it mandates a more aggressive diagnostic and therapeutic strategy than would be used for a healthy individual.

Challenges

Several challenges complicate UTI management post-transplant. Significant drug interactions exist between antibiotics and immunosuppressive medications, which can alter therapeutic efficacy and increase toxicity risks. Infections caused by ESBL-producing strains are associated with a greater clinical and economic disease burden, longer hospital stays, and increased mortality. KTRs may be particularly susceptible to UTIs caused by ESBL-producing *Enterobacterales*. This susceptibility is due to the antimicrobial selective pressure from antibiotic prophylaxis and early empiric treatment for suspected infections. Furthermore, UTIs with ESBL-producing strains can affect transplantation outcomes.[7]

Management

Nitrofurantoin, a first-line antibiotic for uncomplicated UTIs, has an estimated 25 million prescriptions filled worldwide annually.[8]

Pharmacological Profile of Nitrofurantoin

Nitrofurantoin is a redox-active antibacterial agent with the molecular formula $C_8H_6N_4O_5$ and a molecular weight of 238. It is an oral antibiotic belonging to the Nitrofuran class. Nitrofurantoin is a member of the Nitrofuran family, characterized by a furan ring (a 5-membered aromatic ring with 4 carbon atoms and one oxygen atom) directly linked to a nitro group $-NO_2$. It is available in oral forms, including capsules, tablets, and suspension (also known as Furadantin). The typical prescribed dose is 50-100 mg, 4 times daily for 5 days.

Pharmacokinetically, Nitrofurantoin is rapidly absorbed from the gastrointestinal tract with an oral bioavailability of 80-90% (approximately 38.8-44.3%). It has a short half-life of 20 minutes and low binding to plasma proteins or tissues. Nitrofurantoin is quickly eliminated, with 90% excreted through the urine; 25-40% is excreted unchanged in urine, and some is excreted in bile. Its therapeutic effects are restricted to the urinary tract due to this rapid and lack of other systemic activity. Nitrofurantoin can accumulate in urine, where its antibacterial effect is enhanced by acidic pH.

Pharmacodynamically, the antibacterial activity of Nitrofurantoin and its metabolites is enhanced under acidic conditions. Metabolites are formed by bacterial enzyme reduction, but the precise structure and antibacterial properties of each metabolite remain uncertain.[9]

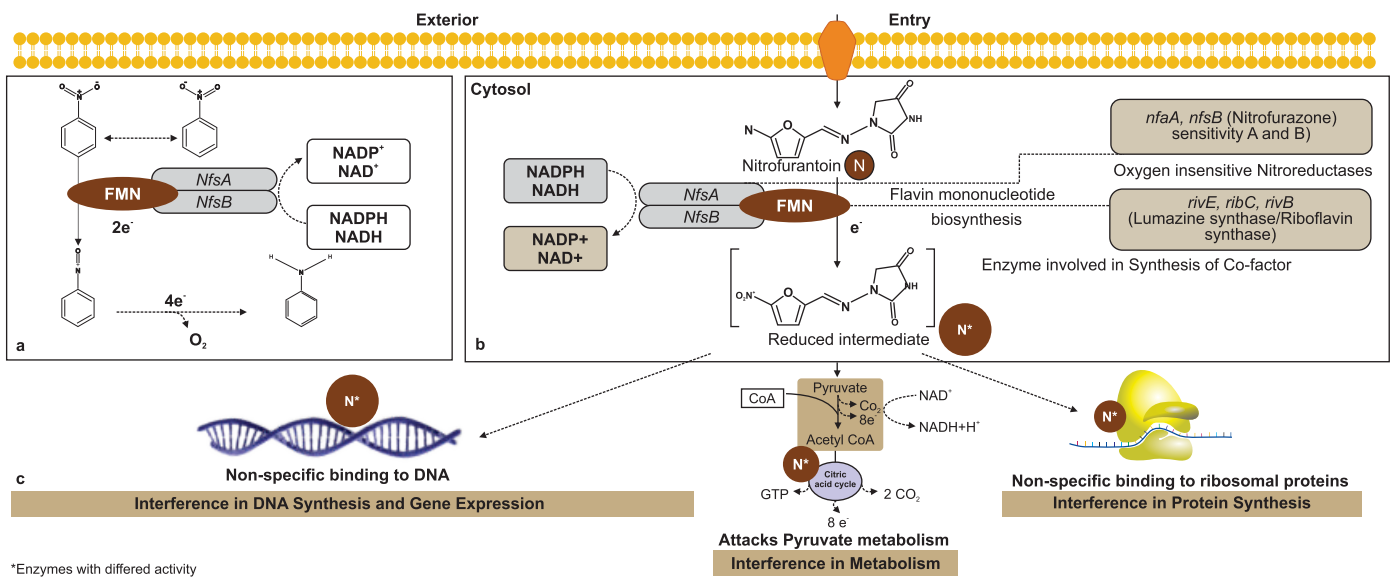
Mechanism of Action

Nitrofurantoin employs several mechanisms for its antimicrobial effect. Bacterial intracellular flavoproteins take up and reduce Nitrofurantoin into reactive intermediates. These metabolites then bind to bacterial ribosomes and inhibit enzymes involved in DNA and RNA synthesis, cell wall protein synthesis, and other metabolic processes. This broad-based mechanism may explain the lack of acquired bacterial resistance. However, mutations in the *nfsA* and *nfsB* genes are potential causes of Nitrofurantoin resistance in *E. coli.*[10]

Administration

According to current Infectious Disease Society of America guidelines, Nitrofurantoin monohydrate/ macro-crystals is recommended as a first-line antibiotic for uncomplicated urinary tract infections.

Fig. 4: Mechanism of Action of Nitrofurantoin[11]



The standard dosage for treating lower UTIs is 100 mg twice daily for 5 days; a 7-day course at the same dosage is also considered acceptable. Treatment durations shorter than 5 days are less effective and are not recommended. For long-term prophylaxis of UTIs, the dosage is 50 mg to 100 mg taken once daily at bedtime.[10]

Use in Specific Patient Populations

Nitrofurantoin is contraindicated for extended use in patients with impaired renal function due to the observation of rare adverse effects such as peripheral neuropathy. It is also contraindicated in patients with bacterial pyelonephritis, anuria, oliguria, or significant renal impairment. Furthermore, Nitrofurantoin is not recommended for treating UTIs in pregnant women at 38–46 weeks of gestation, neonates under one month old, men with prostatitis, and elderly patients over 65 years of age.[11] Its use is contraindicated in neonates and patients with G6PD deficiency due to the risk of hemolysis. It is also contraindicated in patients with a history of cholestatic jaundice or hepatotoxicity.[10]

Impact of Nitrofurantoin on UTI

Uncomplicated UTI is most frequently caused by Uropathogenic *Escherichia coli* (UPEC) strains, which account for 80% of cases. Other causative agents include *Klebsiella pneumoniae, Staphylococcus saprophyticus, Enterococcus spp*., and Group B Streptococcus (GBS). Common symptoms are dysuria, frequency, urgency, suprapubic pain, and hematuria. This infection occurs mostly in women of all ages (50-60%), boys, and the elderly. Predisposing factors include age, level of sexual activity, and pre-existing underlying diseases. Untreated UTI can lead to sepsis with or without pyelonephritis, which has a 10-30% mortality rate and may require hospitalization.

For treatment, conventional antibiotic therapy for acute uncomplicated UTI includes Trimethoprim-Sulfamethoxazole, Cefpodoxime, Cephalexin, Cefuroxime, and Ciprofloxacin. For the acute complicated form, suitable choices are Cefepime, Ampicillin, Imipenem/Cilastatin, and Trimethoprim-Sulfamethoxazole. Long-term use of these conventional antibiotics can lead to the emergence of antibiotic-resistant strains and disruption of the gastrointestinal and vaginal flora.

Fosfomycin and Nitrofurantoin are 2 alternative antibiotics for resistant strains. Nitrofurantoin is more effective than Fosfomycin and shows a greater effect in pregnant women. Oral Nitrofurantoin, in both liquid (25 mg/5 ml) and solid (100 mg) forms, shows an optimum effect for UTI treatment. Studies indicate that oral Nitrofurantoin is the best choice for prophylaxis before surgery and for treating patients over age 12. Therefore, Nitrofurantoin is currently used prophylactically in UTI cases, especially against Vancomycin-sensitive and Resistant strains (VRE and VRS) associated with catheters, as well as Fluoroquinolone and Aminopenicillin-resistant strains. Nitrofurantoin was found to be clinically and microbiologically effective, demonstrating clinical cure rates of 79% to 92% and microbiological eradication rates of 80% to 92%.[9]

Clinical Use of Nitrofurantoin

The clinical efficacy and toxicity of Nitrofurantoin for treating lower UTIs or for prophylaxis were recently evaluated in 2 meta-analyses of controlled trials. An assessment of 27 controlled trials involving 4,807 patients established Nitrofurantoin's effectiveness for UTI treatment, demonstrating clinical cure rates of 79% to 92% and microbiological eradication rates of 80% to 92%. A 7-day treatment course was not more effective than the standard 5-day course, while a 3-day course resulted in diminished clinical efficacy (61%–70%). Toxicity occurred in 5% to 16% of cases, was mild and reversible, and primarily involved gastrointestinal side effects.

An assessment of 26 controlled trials involving 3,052 patients determined that Nitrofurantoin is effective for UTI prophylaxis. Side effects were again noted to be mild, with the risk of severe toxicity increasing with the duration of prophylactic use.[12]

Modified-Release Nitrofurantoin

Nitrofurantoin has traditionally been prescribed for uncomplicated UTIs in adults at an oral dosage of 50–100 mg 4 times daily for 7 days or until 3 days after sterile urine is achieved. To minimize gastrointestinal side effects such as nausea and vomiting, the drug is usually taken with food or milk. To address these limitations and in response to increasing demand from healthcare professionals, a modified-release formulation of Nitrofurantoin (Nitrofurantoin MR) was developed. This formulation offers several advantages over the conventional preparation:

- Reduced dosage frequency from 4 times daily to twice daily.
- Ability to maintain effective urinary concentrations for more than 12 hours.
- Improved gastrointestinal tolerability with fewer incidences of nausea and vomiting.
- Enhanced patient compliance due to less frequent dosing and better tolerability.[13]

A multicentre open study conducted across 45 general practice centres in the UK included 538 patients randomized to receive Nitrofurantoin Modified Release (MR) 100 mg twice daily, Trimethoprim 200 mg twice daily, or co-Trimoxazole 960 mg twice daily for 7 days. Clinical cure was achieved in 87.2% of patients treated with Nitrofurantoin MR, comparable to Trimethoprim (86.5%) and co-Trimoxazole (84.5%).

The bacteriological cure rate for Nitrofurantoin MR (82.3%) was similar to co-Trimoxazole (83.2%) and superior to Trimethoprim (76.8%). For *E. coli* infections, Nitrofurantoin MR achieved a cure rate of 81.5%, while for *non-E. coli* pathogens, it demonstrated equivalence to co-Trimoxazole (86.7%) and outperformed Trimethoprim (72.0%). *In-vitro* sensitivity to Nitrofurantoin was highest at 96.1%, significantly exceeding co-Trimoxazole and Trimethoprim (87.5%, $p<0.01$). Tolerability across all groups was similar; however, drug-related adverse events were fewer with Nitrofurantoin MR (5.6%) compared to co-Trimoxazole (8.8%) and Trimethoprim (7.3%).[14]

Conclusion

UTIs represent a highly significant and complex clinical challenge in renal transplant recipients and patients with CKD, carrying risks of graft dysfunction and loss. Nitrofurantoin is a clinically effective first-line treatment for uncomplicated UTIs, demonstrating high clinical cure and microbiological eradication rates. It is a valuable alternative for resistant strains and is effective for both treatment and prophylaxis. The standard treatment for a lower UTI is 100 mg twice daily for 5 days, as shorter courses diminish efficacy. Optimizing its use in patients with CKD or renal transplants requires balancing its proven efficacy against its contraindication in renal impairment.

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