Management of Urinary Tract Infection in Chronic Kidney Disease: Role of Nitrofurantoin

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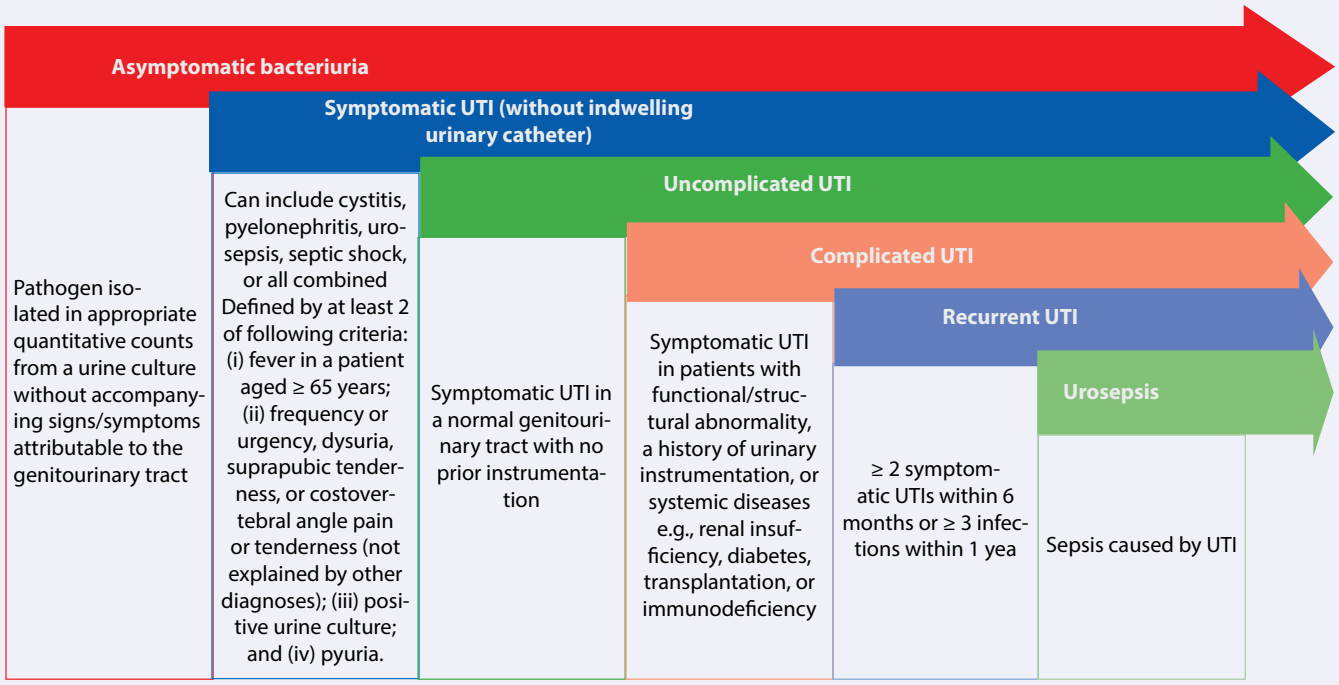
Urinary tract infections: Overview

Urinary tract infections (UTIs) are one of the most common bacterial infections, accounting for millions of visits in clinics and emergency departments each year, and eventually resulting in thousands of hospitalizations.[1] Furthermore, a gender predilection is frequently seen in these visits, with the overall number of office visits for UTIs being twice as common among the women of all ages as compared with the men.

A wide spectrum of clinical scenarios may be seen in cases with UTI, ranging from asymptomatic bacteriuria at one end to sepsis associated with UTI requiring hospitalization at the other end. Figure 1 depicts the wide ranging clinical spectrum of the UTI with associated definition of each phenotype.[1] As evident from this spectrum, a major distinction is often made in UTIs in terms of it being either uncomplicated or complicated. Herein, while the former is defined as a symptomatic UTI in a patient with normal genitourinary tract and no prior instrumentation; the term complicated UTI is used for an infection that occurs in a patient with a structural or functional abnormality of the genitourinary tract that impedes urine flow or in the presence of the underlying diseases. Hence, by this definition, all UTIs in patients with chronic kidney disease (CKD) are considered complicated.

Figure 1: Clinical spectrum of UTIs



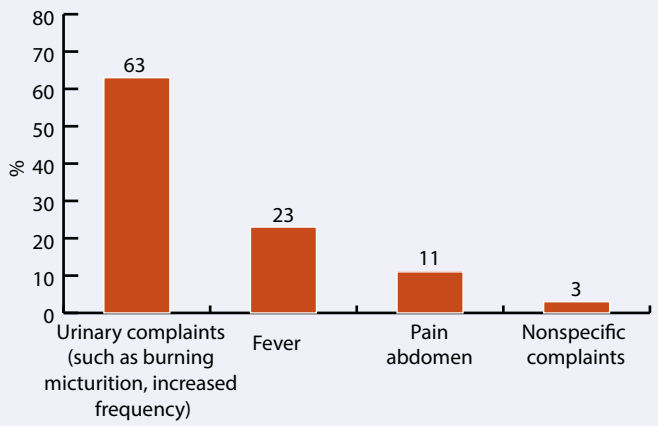
Adapted from: Mody L, Juthani-Mehta M, et al. Urinary Tract Infections in Older Women. A Clinical Review. JAMA. 2014;311(8):844–854.

This short review aims to discuss the management of UTI in CKD patients, and role of nitrofurantoin.

UTI in CKD patients

CKD is emerging as a major public health problem in developing nations like India that already witness the burden of major lifestyle problems like diabetes mellitus and hypertension. Incidentally, many of the CKD patients also have these comorbid/causative conditions, which adds to both financial burden and increase in morbidity.

Figure 2: Common presenting symptoms of UTI in CKD patients



Adapted from: Adapted from: Shankar M, Narasimhappa S, Madhura NS. Urinary Tract Infection in Chronic Kidney Disease Population: A Clinical Observational Study. Cureus. 2021;13(1):e12486.

Furthermore, CKD is also risk factor for developing UTIs mostly due to metabolic abnormalities resulting in alterations in the primary host defense mechanisms.[2,3] Besides, CKD patients frequently undergo instrumentations, and those on prolonged hemodialysis have reduced immunity and are more prone to infections including UTI.[4] In a study of 120 CKD patients from Maharashtra, a high incidence of UTI i.e. 35% was observed.[5] UTI, if left untreated, can progress to worsen the renal function, cause sepsis, septic shock and death.

Generally, UTIs are more common in the women than men, but this may not always hold true in the subgroup of CKD patients. While the study from Maharashtra showed higher rate of UTI in women with CKD, a more recent clinical observational study from south India found that males were most commonly infected.[4,5] The most common presenting symptoms in the South Indian study were urinary complaints such as burning micturition (dysuria), increased frequency of micturition, fever, pain abdomen, and other nonspecific complaints (Figure 2).[4] However, similar to the general population, E. coli (61.8%) was the most common culture grown organism (Figure 3).[4]

Management

The treatment of CKD varies according to patients' underlying disease, the stage of the disease, the speed of decrease in the GFR, and the complications and comorbidities.[6] Considering that the progression of CKD may be related to

Figure 3: Presence of microbial pathogens within the urinary tract in patients with UTI

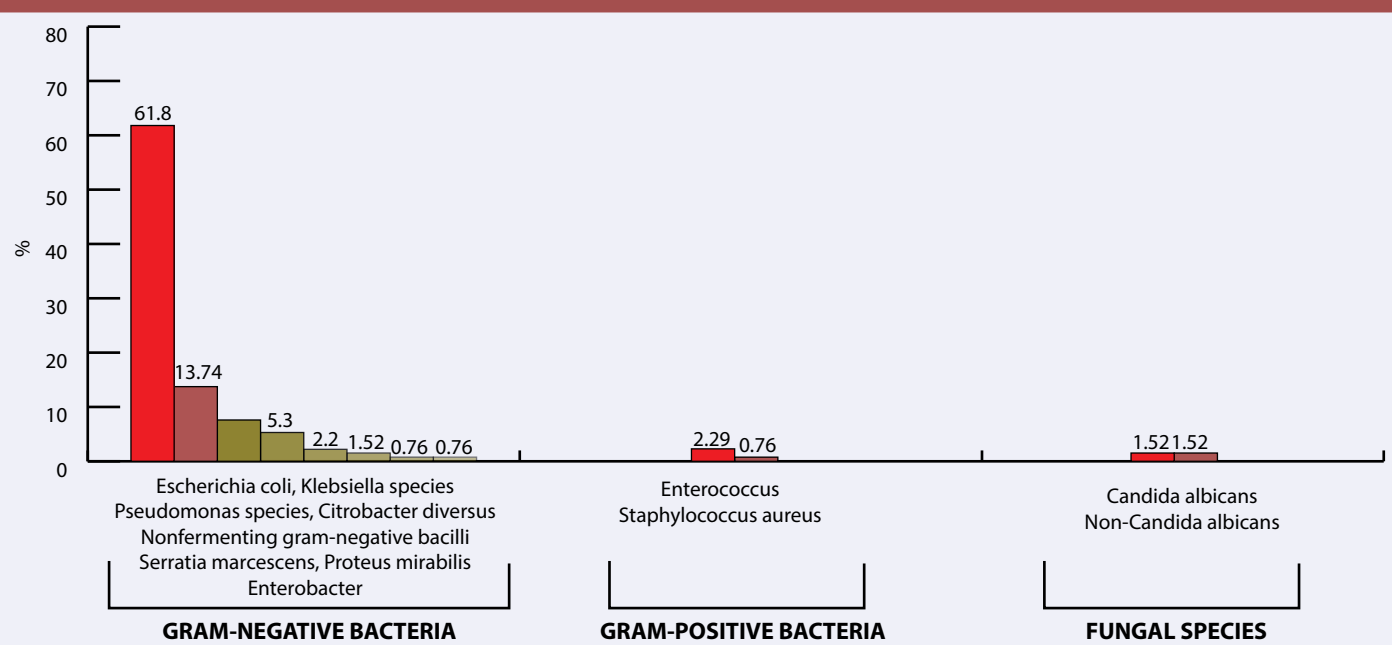


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Table 1: Features of nitrofurantoin	
Characteristic	**Nitrofurantoin**
Year of discovery	1953
Pharmacokinetics	High urinary concentrations Serum concentrations negligible
Mechanism of action	Multifactorial, inhibits ribosomal protein synthesis
Spectrum of activity	Mostly susceptible: E. coli, Enterococcus Variably susceptible: Klebsiella, Enterobacter, Citrobacter and Providencia
Resistance	Uncommon
Adverse events	Infrequent, mainly gastrointestinal
Renal impairment	Contraindicated if CrCl <30 mL/min Cautious use between CrCl 30–60 mL/min if benefits outweigh risks

Adapted from: Gardiner BJ, Stewardson AJ, Abbott IJ, et al. Nitrofurantoin and fosfomycin for resistant urinary tract infections: old drugs for emerging problems. Aust Prescr.2019;42:14–9

recurrent infectious focus, it seems rational that satisfactory management of UTI can improve outcomes, specifically in CKD population.

Nitrofurantoin: An effective alternative with vast experience for UTIs in general population

For several years, trimethoprim-sulfamethoxazole (TMP-SMX) was a preferred antibiotic for the treatment of UTIs. However, development of a high prevalence of TMP-SMX resistance among uropathogens eventually discouraged its use in many communities. Subsequently, the fluoroquinolone class of antibiotics emerged as the next alternative for many clinicians. However, the 2011 Infectious Diseases Society of America (IDSA) guidelines on the treatment of UTIs discouraged use of fluoroquinolones for acute, uncomplicated UTI due to concern of increased prevalence of fluoroquinolone-resistant pathogens that has major implications for the treatment of some more serious infections.[7]

In contrast, nitrofurantoin has been used for decades as an effective alternative treatment of uncomplicated UTIs. The drug has not only retained a high prevalence of sensitivity to most uropathogens, but has a favorable side-effect profile also.[7] Nitrofurantoin hence appears to be a reasonable alternative to both TMP-SMX and fluoroquinolones for empirical treatment of uncomplicated UTIs, especially given the rising prevalence of antibiotic resistance among community uropathogens.

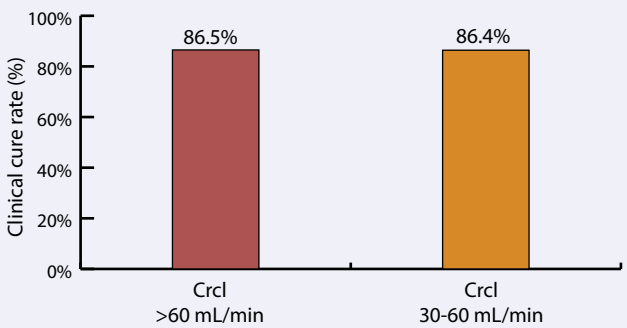
A major strength of nitrofurantoin is its action at multiple sites and levels which helped the drug to maintain an excellent level of sensitivity over 6 decades besides being well tolerated for treating acute uncomplicated cystitis. Data from Pan India also show that not only has nitrofurantoin retained an excellent sensitivity to the most common uropathogens across India, but also stands out to be an antimicrobial of choice when considering other parameters like oral route of administration, safety profile and cost-effectiveness in the management of UTIs.[8] Another advantage of nitrofurantoin is a virtual lack of collateral damage to commensal microbiota. Evidence in this regard supports use of nitrofurantoin over fluoroquinolones for treatment of uncomplicated UTIs to minimize perturbation of intestinal microbiota.[9] Table 1 depicts features of nitrofurantoin that make it a preferred option for patients with UTIs.[10]

Nitrofurantoin for UTI in patients with renal impairment: GFR considerations?

The therapeutic concentrations of nitrofurantoin are achieved only in the urine, and the drug is eliminated primarily by glomerular filtration. Therefore, renal elimination of nitrofurantoin is reduced in patients with low estimated GFR (eGFR), with consequent risk of treatment failure for UTI and possibly also the risk elevated blood concentrations and toxicity.[11]

Historically, nitrofurantoin was hence thought to be contra indicated if the creatinine clearance (CrCl) was <60mL/minute. However, this recommendation remains controversial. Rather, recommendations have now been changing to allow a cautious, short-term use in patients with mild renal impairment (30–60 mL/min).[10] Emerging data suggest that the presence of mild or moderate reductions in eGFR may not justify avoidance of nitrofurantoin.[11] In a retrospective cohort study in older patients (aged ≥65 years) with renal

Figure 4: Clinical cure rate with nitrofurantoin in cystitis and variable degree of renal dysfunction



Adapted from: Welch E, Sheth S, Ashong CN, et al. Retrospective Review on the Safety and Efficacy of Nitrofurantoin for the Treatment of Cystitis in the Veteran Population With or Without Renal Insufficiency. *Open Forum Infect Dis*. 2021;8(9):ofab442.

impairment and UTI nitrofurantoin prescribing was not associated with an increased risk of adverse outcomes in patients with an eGFR <60 mL/minute/1.73 m^2.[12] Recently, another retrospective chart review compared the efficacy and safety of nitrofurantoin for the treatment of cystitis in males and females with variable degrees of renal dysfunction, and found that clinical cure rate did not vary between patients with a CrCl >60 mL/min compared with those with CrCl 30–60 mL/min (86.5% vs. 86.4%; Figure 4).[13] Evidence in fact suggest that the drug be avoided only for those with eGFR below 40 mL/min per 1.73 m^2, and in those with CrCl at least 40 mL/min/1.73 m^2, it can be safely administered.[1,11,14] It should be further noted that administration of nitrofurantoin with food would result in higher urinary concentrations.[10]

Conclusion

Urinary tract infection are common in general practice, and more so in the specialty of Nephrology. These infections may have wide clinical spectrum ranging from asymptomatic bacteriuria to urosepsis. Another common condition seen in nephrology care in the presence of renal insufficiency, which could be both functional (in older patients) or organic (in patients with CKD). CKD patients often have various other comorbidities also like diabetes and hypertension, and this combination further accentuates the proneness of CKD patients for UTIs. Nitrofurantoin has remained a preferred alternative for patients with uncomplicated UTIs owing to high efficacy and low resistance pattern. In CKD patients, historically, there was a concern that use of nitrofurantoin be contraindicated in renal insufficiency patients with eGFR<60. However, this concern seemed to based on limited data, and hence with emerging evidence, it is recommended that nitrofurantoin can be safely administered in patients with CrCl at least 40 mL/min/1.73 m^2. Regardless, a caution based on patients' clinical condition and physicians' discretion would always be appreciated in favor of increased patient safety.

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