Current Approaches to Febrile Urinary Tract Infections in Adults

Reviewed by:
Dr. Atul Gogia
MBBS,DNB,MRCP (UK)
Consultant Physician
Department of Medicine
Sir Ganga Ram Hospital
New Delhi

Urinary Tract Infection: An Overview

Urinary tract infection (UTI) is the third most common infectious disease seen in individuals after respiratory and gastrointestinal infections. UTI is known as an inflammatory response to colonization of urinary tract including the lower and the upper urinary tract by microbial pathogens; most commonly bacteria. These bacterial intruders or uropathogens intend to cause adhesions, release siderophores and toxins within the urinary tract giving rise to plenty of urinary and systemic signs and symptoms. The infection is found to be prevalent among men and women but it shows a predilection for women owing to their distinct anatomy and reproductive physiology. Adult women of all ages have increased susceptibility to UTIs, with an incidence ratio of 8:1 as compared to men. In older adults (> 65 years), UTIs are the second most common cause of infectious disease hospitalization, after lower respiratory tract infections.[1-7]

A variety of parameters tends to intensify the risk of UTIs, such as age, parity, gravidity, pregnancy, underlying urologic abnormalities, and association of diseases contributing to the increased virulence and bacterial overload including diabetes, multiple sclerosis, acquired immunodeficiency disease syndrome and patients with catheters and /or spinal cord injuries. It's widespread prevalence also accounts for utilization of large amount of healthcare resources, imposing a huge financial constraint.[2,4]

The clinical features of UTI include painful voiding, dysuria, polyuria (frequent urination), urinary urgency, nocturia (urination during night), hematuria (urine with traces of blood), fever and flank pain (Figure 1).[8]

Classifications of UTI

Conventionally, UTIs have been classified depending on the anatomic site of involvement into lower and upper urinary tract infections. The infections of the lower urinary tract include cystitis, urethritis, prostatitis, and epididymitis, and those of the upper urinary tract include pyelonephritis.[9]

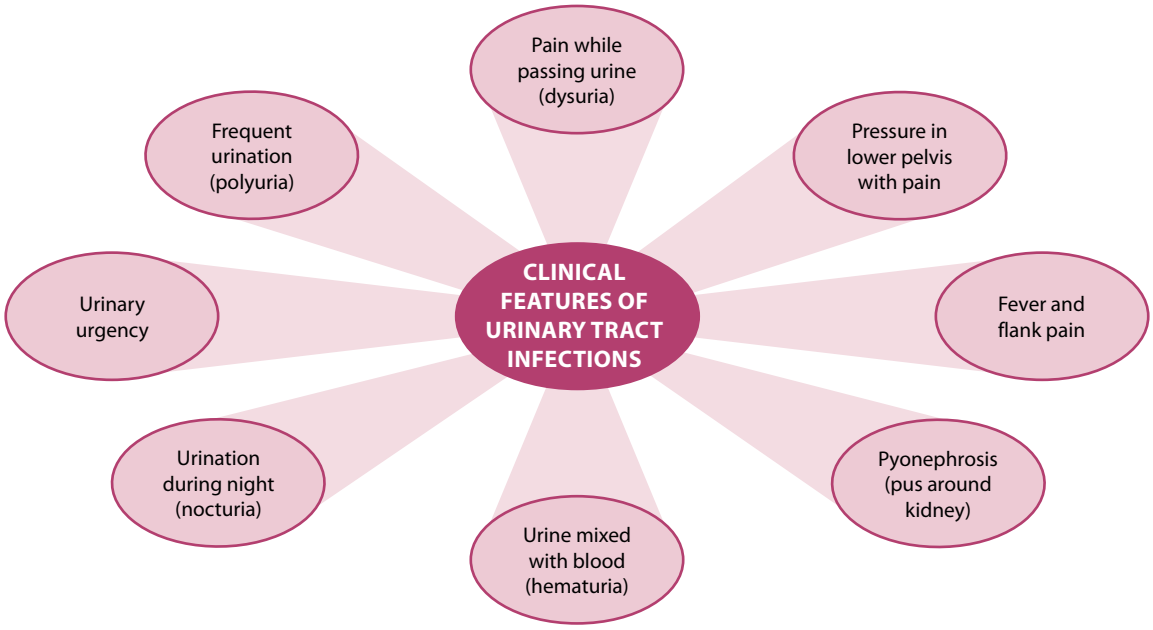
UTIs can be further classified as complicated and uncomplicated UTI. Complicated UTI occurs when there is structural or functional irregularity in the genitourinary tract. Uncomplicated UTI manifests in premenopausal, non-pregnant women with no known anatomical or functional urological abnormalities or other comorbidities.[9-11]

However, some researchers consider UTIs in postmenopausal women or women with well controlled diabetes mellitus without urological sequelae also to be 'uncomplicated'. Considering these various classifications of UTIs, it seems reasonable to classify these patients uniformly according to their presentation, in which fever reflects the presence of a parenchymal inflammation.[10-11]

Febrile UTI: Fever as an Important Symptom in Urinary Tract Infections

It may appear interesting to know the anatomical distinction of UTI, whether the UTI involves the kidney, prostate, bladder, blood circulation, lymph nodes of the pelvis or a combination of all; however, from a clinical point of view, febrile UTI should be considered tissue inflammation of the urinary tract, whereas an exact anatomical distinction on clinical grounds can often not be made. Therefore, febrile UTI may be considered the clinical syndrome of interest, defined as UTI accompanied by fever, irrespective of the presence or absence of flank pain or tenderness; fever mainly determines the appropriate treatment. In sync with the above mentioned

Figure 1: Clinical features of urinary tract infections



classifications, febrile UTI may include complicated UTI with fever, acute prostatitis, acute uncomplicated pyelonephritis and, the urosepsis syndrome.[10-12]

Interestingly, although fever is supposed to be a prominent feature in upper UTI including pyelonephritis, evidence suggests the presence of fever in lower UTIs also, such as acute bacterial prostatitis, chronic bacterial prostatitis, and cystitis.[1,13-15] Moreover, presence of fever, besides worsened urinary urgency or frequency, acute dysuria, suprapubic tenderness, or costovertebral angle pain or tenderness, constitutes an important clinical diagnostic criterion for uncomplicated symptomatic UTI.[16] Among older adults also, fever and localized urinary symptoms are considered the initial trigger for UTI evaluation.[5]

Understanding Pathogenesis of UTI

The uropathogen invasion in the urinary tract is headed by three routes namely, ascending, hematogenous and lymphatic route.[17] Once the uropathogen makes its way towards the urinary tract, it adheres to the tissues followed by certain pathophysiological changes and thereby withstands the flow of urine. The uropathogens colonize and flourish in the periurethral region and later ascend into the bladder resulting in symptomatic or asymptomatic bacteriuria.[18] The pathophysiological changes give rise to a variety of clinical manifestations in the affected patient.[8]

The inflammatory process is considered one of the contributory factors for fever in UTIs. In fact, inflammation has been found to have a direct effect on bladder function. In cases of acute inflammation, such as in UTI, the inflammatory mediators are released and cause urothelial injury and bladder wall irritation. These inflammatory changes are accountable for clinical manifestation of urgency, dysuria, frequency, nocturia, and fever.[15]

In men with febrile UTI, a transient increase in prostate volume and serum prostate-specific antigen (PSA) has been observed during the acute stage, suggestive of a concurrent infection of the prostate.[21] Men with fever and UTI have similar findings of prostatic involvement, irrespective of prostatic tenderness. This suggests that infection is solely or also taking place within the prostate itself, unrelated to a diagnosis of acute pyelonephritis or acute prostatitis.[20]

Microbial Etiology of UTI

Two microorganisms are responsible for 80-95% of uncomplicated UTIs, with *E. coli* being responsible for 80% and *Staphylococcus saprophyticus* for another 5-15% cases. Enterococcus, *Proteus mirabilis*, Klebsiella species, and Pseudomonas species account for the remaining

5–10% of UTIs. In contrast, a variety of pathogens are implicated in complicated UTIs, with only 34.5% being caused by *E. coli*. Other relatively common microorganisms causing complicated UTIs are; *Streptococcal faecalis* (16%), *Staphylococcus epidermidis* (13%), *Proteus mirabilis* (13%), *Pseudomonas* spp. (5%), *Staphylococcus aureus* (4%), Enterobacter spp. (2.5%), Serratia spp. (1.5%), Streptococcus spp. (1.5%), Acinetobacter spp. (1.5%) and Citrobacter spp. (1.0%).[21] A prospective study[19] of 85 men (median age, 63 years) revealed that *E. coli* comprised 66 (78%) of the febrile UTI isolates.

Management Strategies for UTIs in the Era of Antimicrobial Resistance

Since UTI is one of the most common bacterial infections encountered among masses, the use of anti-infective agents to counteract the rising infection has been a frontline strategy.[20] Antimicrobial therapy aims at eliminating the bacterial growth in the urinary tract through the use of antibiotics, which are well-tolerated, effective, and economic.[23] It is well known that appropriate antibiotic therapy leads to higher rates of symptomatic relief and bacterial eradication in patients with uncomplicated UTI.[24]

However, it has been evident that empirical antimicrobial treatment is initiated in most of the cases before the laboratory results of urine culture are obtained. This frequent misuse of drugs has significantly contributed to the rising problem of antimicrobial resistance, which has made the treatment complicated and challenging. It has been reported that *E. coli*, the most commonly implicated pathogen in urinary tract infections has become resistant to several antibiotics including fluoroquinolones, trimethoprim/sulfamethoxazole, penicillins, and cephalosporins.[25-29]

The World Health Organization (WHO) report shows high levels of *E. coli* resistance to fluoroquinolones and third generation cephalosporins, including in South-East Asia Region, which is home to a quarter of the world's population. Thus, the rising antimicrobial resistance mandates the need for an optimal therapeutic agent. Selection of such an agent must take into account local resistance patterns, patient-specific factors, severity of disease, and pharmacokinetic and pharmacodynamic principles. In this context, nitrofurantoin has emerged as a drug of choice, with good efficacy and favorable tolerability profile.[28-32]

Combating Urinary Tract Infections: Focus on Nitrofurantoin

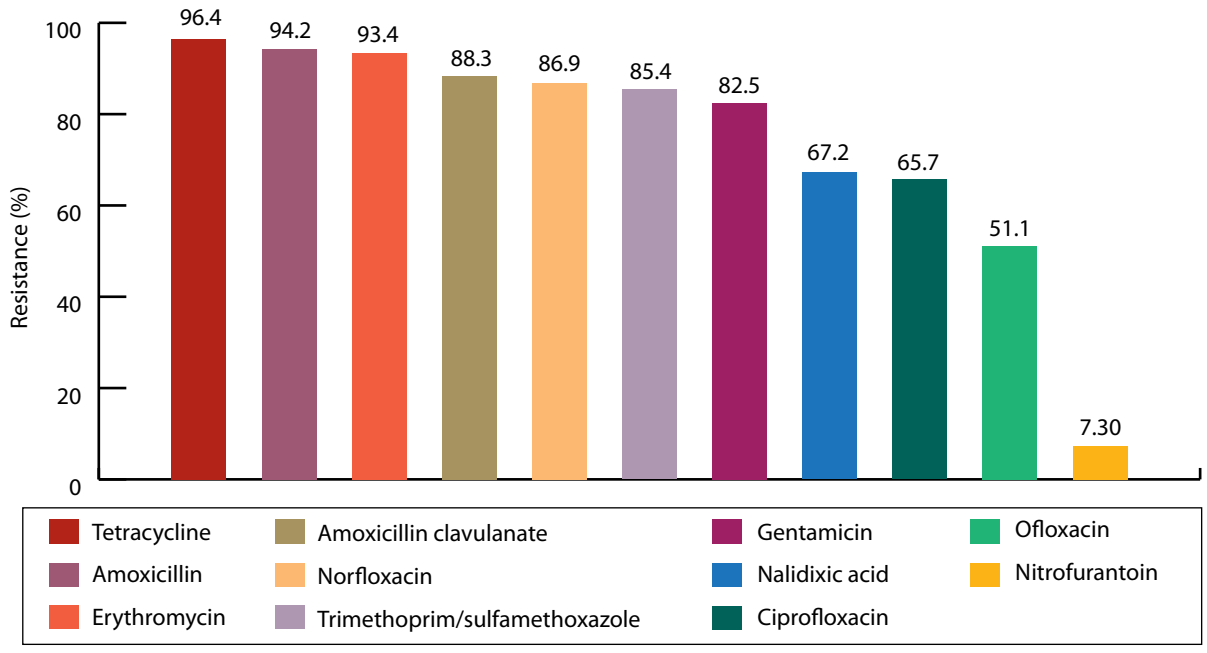
Nitrofurantoin has a unique mechanism of action. It mainly acts by inhibiting various bacterial enzymes that participate in bacterial carbohydrate metabolism at three different locations in the Krebs cycle. In addition, it also interferes with cell wall synthesis. Nitrofurantoin acts by undergoing reduction by bacterial nitroreductases to produce toxic derivatives that attach to ribosomal proteins and cause defective transcription and translation in bacteria.[33-35] Furthermore, the pharmacokinetic properties such as pH dependent resorption at normal urinary pH (approximately 5.5 pH); excretion primarily into the lower urinary tract, i.e., bladder urine, renders it a beneficial agent in the treatment of urinary tract infections.[34] In addition, this drug displays advantages in terms of site specificity and attainment of high urinary levels. It is rarely associated with any adverse events, thus presenting an excellent tolerability profile.[36] Another property of this drug that makes it a suitable agent in the management of urinary tract infections is minimal resistance to pathogens.[33,36]

Antimicrobial Spectrum of Nitrofurantoin

Nitrofurantoin encompasses a broad antibacterial spectrum and the drug is particularly effective against the main uropathogens. Nitrofurantoin is active against *E. coli*, Enterococci, *S. aureus*, *Klebsiella pneumonia*, Enterobacter species, Citrobacter species, group B Streptococci and most strains of multidrug-resistant Gram-negative bacilli.[35,37,38] Nitrofurantoin is gaining prominence in the management of UTIs due to increasing incidence of resistance against other commonly used antibiotics, such as trimethoprim/sulfamethoxazole (TMP/SMX), resulting in treatment failures.[37] Interestingly, a study by Olorunmola and coworkers[39] revealed high sensitivity of nitrofurantoin in comparison with other antibiotics to *E. coli* isolates from cases of UTI. The findings revealed widespread resistance of the isolates to all the antibiotics (51.1-96.4%), except nitrofurantoin that showed a low resistance rate of 7.3% (Figure 2).

Similar outcomes have also been reported from studies conducted in Indian patients with urinary tract infections.[40] The investigators of one such study demonstrated that *E. coli* was the most frequently isolated microbe accounting for 61.84% of the total isolates. Moreover, majority of *E. coli* strains were resistant to various antibiotics such as ampicillin (>80%), amoxiclav (>80%), co-trimoxazole

Figure 2: Resistance of E. Coli to different antibiotics



(>67%), nalidixic acid (>95%), norfloxacin (>77%), and ciprofloxacin (>74%). However, nitrofurantoin was reported as the drug with least resistance (>5-6%) to *E. coli* throughout the study duration of 30 months.[40] Another study by Dash and colleagues[25] reported nitrofurantoin to be one of the most active antimicrobial drugs with low resistance to uropathogens in Indian patients with urinary tract infections.

Modified Release Nitrofurantoin

Modified release formulation should be preferred over conventional and sustained release formulations, as modified release nitrofurantoin provides release of initial loading dose in beginning to achieve desired MIC levels. This is followed by release of maintenance dose, which releases constantly over period of time to maintain adequate urinary concentration. Loading dose ensures no risk of treatment failure. It has been seen that modified release nitrofurantoin formulation provides better GI tolerance when compared to conventional and plain nitrofurantoin tablets.[41]

Advantages of modified release nitrofurantoin are discussed in Box 1.

The recommended dosage of nitrofurantoin by the Infectious Disease Society of America (IDSA) and the European Society for Microbiology (2010) is 100 mg twice-daily for 5 days for treating acute uncomplicated cystitis in women.[11] The American College of Obstetricians and Gynecologists recommends a 7-day, four times a day regimen of nitrofurantoin 50 to 100 mg or a 7-day, twice-daily regimen of nitrofurantoin 100 mg for treating non-pregnant women with uncomplicated acute bacterial cystitis.[42]

Box 1: Advantages of modified release nitrofurantoin

- Advantages of loading dose and maintenance
- Offers twice-daily dosage schedule with better GI tolerability
- Recommended as a first-line therapy in lower UTI
- Better patient compliance
- Approved by US Food and Drug Administration (USFDA)
- Indicated in uncomplicated lower UTI, recurrent cystitis related to coitus
- Safe for long-term usage (up to 12 months) in prophylaxis

Evidence-Based Efficacy of Nitrofurantoin in Patients with Urinary Tract Infections

Owing to its clinical efficacy, minimal resistance to uropathogens, and minimal propensity for collateral damage, nitrofurantoin has been recommended by several international guidelines (Infectious Diseases Society of America, European Society for Microbiology and Infectious

Figure 3: Sensitivity rate of E. Coli to nitrofurantoin

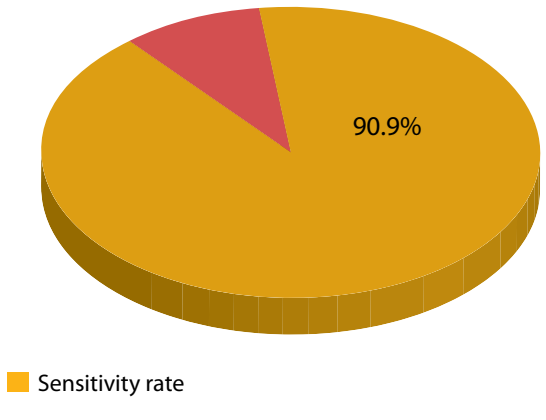
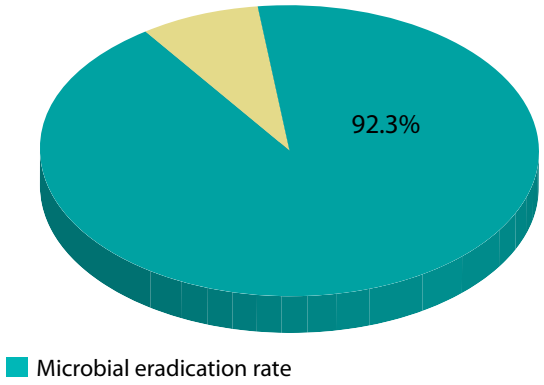


Figure 4: Rate of microbial eradication on treatment with nitrofurantoin in patients with urinary tract infections



Diseases, European Association of Urology, and Scottish Intercollegiate Guidelines) as a first-line drug for the treatment of uncomplicated urinary tract infections.[33,43]

According to the Guideline on Urological Infections by the European Association of Urology, nitrofurantoin is one of the most effective antimicrobial agents for prophylaxis in children with febrile UTI.[44] Moreover, as majority of men with febrile UTI have a concomitant infection of the prostate, the goal is not only to sterilize the urine but also to eradicate the prostatic infection.[20] Herein, a long course (4–12 weeks) of effective antimicrobial therapy is considered the most important part of the treatment strategy for chronic bacterial prostatitis. In case of treatment failure by trimethoprim and fluoroquinolones, longer-term (three to six months) antimicrobial prophylaxis using nitrofurantoin (50–100mg/day) is often recommended.[13]

Data available from several studies provides evidence in favor of its efficacy in the management of urinary tract infections. In a study by Kumar and coworkers,[45] nitrofurantoin displayed sensitivity to about 90.9% of the *E. coli* isolates from patients with urinary tract infections (Figure 3). A comparative study assessed the susceptibility of antimicrobial resistant urinary *E. coli* isolates to fluoroquinolones and nitrofurantoin for duration of 3 years. The results showed that 9.5% were resistant to ciprofloxacin while only 1.9% were resistant to nitrofurantoin.[46] In another study, Mendoza-Valdes A *et al*[47] analyzed the antimicrobial and clinical efficacy of nitrofurantoin in the treatment of urinary tract infections in certain parts of the world, where resistance rates of uropathogens to trimethoprim/sulfamethoxazole are high. In this open-label, single-arm study, adult patients with positive urine culture were enrolled. The primary endpoint analysis revealed a microbial eradication rate of 92.3% on administration of nitrofurantoin (Figure 4). At 35 to 42 days, the eradication rate was 83.3%. Moreover, urinary nitrofurantoin concentrations were mostly above minimum inhibitory concentrations of the isolated uropathogens. The drug was generally well tolerated. These findings indicate good antimicrobial and clinical efficacy of nitrofurantoin in the treatment of urinary tract infections as well as acceptable tolerability in adults.

Conclusion

Urinary tract infection is a diverse clinical entity and one of the most challenging infectious disorders and is considered a major reason for which the patients seek medical care. Febrile urinary tract infection is considered a clinical syndrome that may be defined as UTI accompanied by fever, irrespective of the presence or absence of flank pain or tenderness; fever mainly determines the appropriate treatment. Although a wide range of bacterial organisms are implicated in their development, *E. coli* strains are responsible for up to 90% of the infections. This necessitates the need for implementation of an appropriate therapeutic strategy. The use of antimicrobial agents has been a corner stone in the management of urinary tract infections. The objective of antimicrobial therapy is to eradicate the infecting organisms from the urinary tract and provide the resolution of symptoms. In the light of increasing resistance to antibiotics used for the treatment, nitrofurantoin is considered a promising drug. Moreover, nitrofurantoin is also an effective therapeutic option for prophylaxis of urinary tract infections as it is

well tolerated, with the added advantage of minimal resistance, less susceptibility for collateral damage, and low propensity to induce development of drug resistance.

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