Choice of Antibiotics in Patients with Urinary Tract Infection

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Urinary Tract Infections: A Common Cause for Seeking Medical Care

Urinary tract infections (UTIs) are among the most common bacterial infections, affecting 150 million people each year worldwide. UTIs are a significant cause of morbidity in infant boys, older men and females of all ages. Serious sequelae include frequent recurrences, renal damage in young children, and complications caused by frequent antimicrobial use, such as high-level antibiotic resistance and Clostridium difficile colitis.[1]

Prevalence of Urinary Tract Infections

UTIs are very frequent bacterial infections in women. These are seen more often in women than in men (8:1), with approximately 50-60% of women reporting at least one incidence in their lifetime. The incidence of UTI increases with age and sexual activity. Post-menopausal women have higher rates of UTIs because of pelvic prolapse, lack of estrogen, loss of lactobacilli in the vaginal flora, increased periurethral colonization by Escherichia coli (E. coli), and a higher incidence of medical illnesses such as diabetes mellitus (DM).[2-5]

Classifications of Urinary Tract Infections

UTI in adults can be categorized into five groups: women with acute uncomplicated cystitis, women with recurrent cystitis, women with acute uncomplicated pyelonephritis, complicated UTI, and asymptomatic bacteriuria (Box 1).[6]

Uncomplicated UTIs usually affect individuals who are otherwise healthy and have no structural or neurological urinary tract abnormalities; these infections are differentiated into lower UTIs (cystitis) and upper UTIs (pyelonephritis). Complicated UTIs are defined as UTIs associated with factors that compromise the urinary tract or host defence.[1]

Causes of Urinary Tract Infections

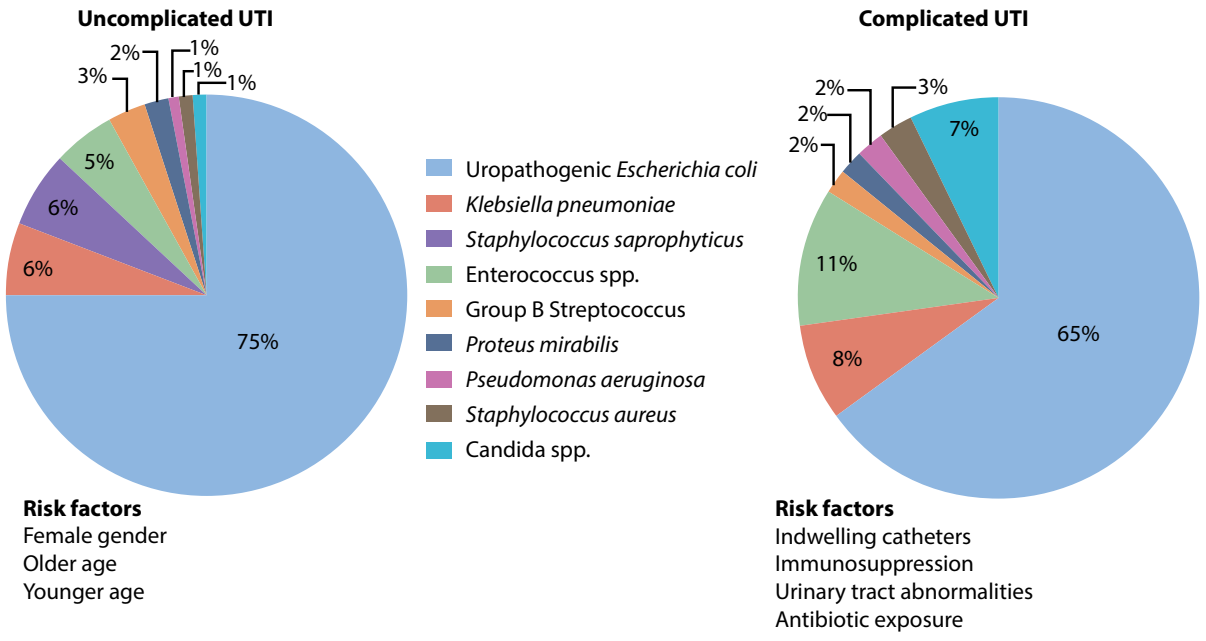
UTIs are caused by a wide range of pathogens, including Gram-negative and Gram-positive bacteria, as well as fungi. The most common causative agent for both uncomplicated and complicated UTIs is uropathogenic *Escherichia coli* (UPEC). For uncomplicated UTIs, other causative agents are *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*,

Box 1: Categories of urinary tract infections in adults

- Acute uncomplicated cystitis in healthy women
- Recurrent acute uncomplicated cystitis in healthy women
- Acute uncomplicated pyelonephritis in healthy women
- Asymptomatic bacteriuria
- Complicated urinary tract infection
  - Male sex
  - Pregnancy
  - Poorly controlled diabetes
  - Obstruction or other structural factor (Urolithiasis, malignancies, ureteral and urethral strictures, bladder diverticula, renal cysts, fistulas, ileal conduits, other urinary diversions)
  - Functional abnormality (Neurogenic bladder, vesicoureteral reflux)
  - Foreign bodies (Indwelling catheter, ureteral stent, nephrostomy tube)
  - Other conditions (Renal failure, renal transplantation, immunosuppression, multidrug-resistant uropathogens, health care–associated (includes hospital-acquired/ LTCF-acquired) infection, prostatitis-related infection, upper tract infection in an adult other than a healthy woman, other functional or anatomic abnormality of urinary tract)

Adapted from: Hooton T. Urinary Tract Infections in Adults. In: Feehally J, Floege J, Tonelli M, Johnson RJ, eds. Comprehensive Clinical Nephrology. 6th edition. Elsevier; 2019: 626-638.

Figure 1: Causative pathogens and risk factors for urinary tract infections



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Enterococcus faecalis, group B *Streptococcus* (GBS), *Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus* and Candida spp. For complicated UTIs, the other causative agents are Enterococcus spp., *K. pneumoniae*, Candida spp., *S. aureus, P. mirabilis, P. aeruginosa* and GBS (Figure 1).[1] Pathogenic bacteria ascend from the perineum, causing UTI. Women have shorter urethras than men and therefore are more susceptible to UTI.[2]

Diagnosis of Urinary Tract Infections

The diagnosis of acute uncomplicated cystitis can be made with high probability based on a focused history of lower urinary tract symptoms (dysuria, frequency and urgency) in a patient who has no risk factors for complicated UTI. Urine dipstick analysis, as opposed to urinary microscopy, is a reasonable alternative to urine culture to diagnose acute uncomplicated cystitis. Urine cultures are recommended for patients with risk factors for complicated UTIs and in certain conditions, such as suspected acute pyelonephritis and symptoms that do not resolve or recur within 2–4 weeks after completion of treatment.[7]

Management of Urinary Tract Infections

Antibiotic options available for use in urinary tract infections

Simple uncomplicated cystitis responds very well to oral antibiotics.[7] Trimethoprim/Sulfamethoxazole for 3 days is good mini-dose therapy, but resistance rates are high in many areas. Nitrofurantoin is a good choice for uncomplicated UTI; it is bacteriostatic and must be used for 5 to 7 days. Fluoroquinolones have high resistance (Table 1).[2,6,8-10]

Effect of renal impairment on course of infections

Around 6% of adults in the developed nations have an estimated glomerular filtration rate (eGFR) of <60 mL/minute/1.73 m^2. This increases with age to around 20% of those aged ≥65. There is increasing evidence of an association between renal impairment and infection. Older patients with renal impairment presenting to primary care with a UTI have been found to have an increased risk of UTI-related hospitalisation and death, suggesting a need for interventions that reduce the risk of these adverse outcomes.[11]

Effect of renal impairment on antibiotics action and pharmacokinetics

The efficacy of antibiotics depends on their concentration relative to the minimum inhibitory concentration (MIC) of the culprit bacteria. Kidney disease can cause wide-ranging changes in pharmacokinetics through derangement of not only kidney drug clearance but also, non-renal clearance, volume of distribution and bioavailability. Therefore, dose adjustments may be required for selected drugs with pharmacokinetics that change significantly in kidney disease, particularly if there is a high risk of drug accumulation and severe and/or irreversible toxicity.[12]

Table 1: Antimicrobial agents for the management of urinary tract infections

CHOICE OF THERAPY	DRUG	DOSAGE	COMMENTS
First	Nitrofurantoin	100 mg twice daily for five days	• Bacteriostatic • Devoid of acquired bacterial resistance
	Trimethoprim/ sulfamethoxazole (TMP-SMX)	160/800 mg twice daily for three days	• High resistance rates in certain cases • If used in pregnancy (not approved use), avoid in first trimester
	Fosfomycin	3-g single dose	• Less effective than fluoroquinolone or TMP-SMX • Lower clinical cure rate compared with nitrofurantoin
Second	Ciprofloxacin	250 mg twice daily for three days	• Although effective, fluoroquinolones should be considered second-line treatment to preserve their usefulness for other infections • Risks of systemic fluoroquinolone antibacterial drugs may outweigh their benefits for uncomplicated cystitis
	Levofloxacin	250 mg once daily for three days	
	Ofloxacin	200 mg once daily for three days *or* 400-mg single dose	
Third	Amoxicillin/ clavulanate	500/125 mg twice daily for seven days	• Not recommended for initial treatment because of concerns about resistance • Inferior to ciprofloxacin in 3-day regimen
	Cefpodoxime	100 mg twice daily for seven days	

Adapted from: References 2,6,8-10

Nitrofurantoin: Role in Urinary Tract Infections

Nitrofurantoin is an antibiotic medication that is used for the treatment of uncomplicated lower UTI. It is effective against most Gram-positive and gram-Negative pathogens. Several major guidelines have declared nitrofurantoin as the first-line therapy for the treatment of uncomplicated lower UTIs. Increasing resistance to newer antibiotics coinciding with increasing prevalence of extended-spectrum beta-lactamase (ESBL) producing bacteria has led to resurgence in use of nitrofurantoin.[13] Nitrofurantoin has 80% oral bioavailability, and approximately 25% is excreted unchanged in the urine, with only a small portion reaching the colon. Administration with food results in higher urinary concentrations and fewer gastrointestinal adverse effects. Nitrofurantoin concentrates in the lower urinary tract while maintaining a low serum concentration and also does not significantly affect bowel flora. Also, it is promptly excreted in urine and very low levels are found in tissues; these features make it an excellent antibiotic choice (Box 2).[7,9,10,13]

Nitrofurantoin is reduced by bacterial flavoproteins to reactive intermediates which inactivate or alter bacterial ribosomal proteins and other macromolecules. As a result of these inactivations, the vital biochemical processes of protein synthesis, aerobic energy metabolism, DNA synthesis, RNA synthesis, and cell wall synthesis are inhibited. This broad-based mode of action may explain the lack of acquired bacterial resistance to nitrofurantoin, as the necessary multiple and simultaneous mutations of the target macromolecules would likely be lethal to the bacteria.[10]

Box 2: Advantages of nitrofurantoin in treatment of urinary tract infections

- Oral bioavailability ≈ 80%
- Concentrates in the lower urinary tract
- Low serum concentration
- Does not significantly affect bowel flora
- Promptly excreted in urine
- Very low levels are found in tissues
- Devoid of acquired bacterial resistance

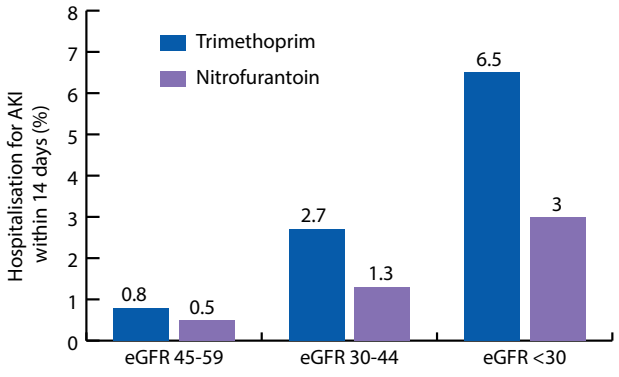
Adapted from: References 7,9,10,13

Evidence-Based Efficacy of Nitrofurantoin in Urinary Tract Infections

Older adults with impaired kidney function are at increased risk of hospitalisation or death following a UTI. In this context, Ahmed and colleagues[11] conducted a study to determine the risk of adverse outcomes in patients aged 65 years presenting to primary care with a UTI, by eGFR and empirical prescription of nitrofurantoin versus trimethoprim.

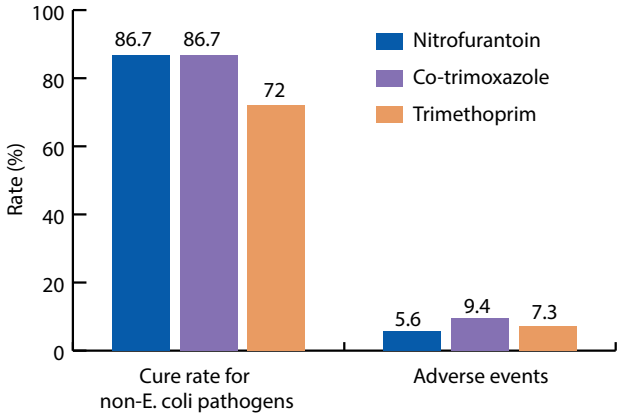
Compared to an eGFR of >60 mL/minute/ 1.73 m^2, patients with an eGFR of <60 mL/minute/1.73 m^2 had greater risk of UTI-related hospitalisation and acute kidney injury (AKI). Importantly, compared to trimethoprim, nitrofurantoin prescribing was associated with lower risk of hospitalisation for AKI (Figure 2). Findings of this study suggest that older adults with impaired kidney function who are treated with nitrofurantoin may not be at greater risk of an adverse outcome and are less likely to experience a

Figure 2: Rate of hospitalization for acute kidney injury with trimethoprim versus nitrofurantoin in patients presenting with urinary tract infection



Adapted from: Ahmed H, Farewell D, Francis NA, et al. Risk of adverse outcomes following urinary tract infection in older people with renal impairment: Retrospective cohort study using linked health record data. *PLoS Med.* 2018;15(9):e1002652.

Figure 3: Cure rate and adverse events with various medications in patients with urinary tract infection



Adapted from: Spencer RC, Moseley DJ, Greensmith MJ. Nitrofurantoin modified release versus trimethoprim or co-trimoxazole in the treatment of uncomplicated urinary tract infection in general practice. *J Antimicrob Chemother*. 1994;33 Suppl A:121-9.

hospital admission for worsening kidney function. Therefore, nitrofurantoin prescription could be used in selected patients with moderate-severe renal impairment.[11]

In another study, Spencer *et al*[14] compared the efficacy and safety of nitrofurantoin modified release (MR) with co-trimoxazole and trimethoprim in patients (n=538) presenting with one or more symptoms of uncomplicated UTI. Whilst the bacteriological cure rate for Escherichia coli infection was similar; for non-E. coli pathogens, nitrofurantoin MR was equivalent to co-trimoxazole with 86.7% cure but higher than trimethoprim at 72.0%. In-vitro sensitivity to all pathogens isolated at baseline was very high for nitrofurantoin at 96.1%, significantly higher than either co-trimoxazole or trimethoprim at 87.5%. Of note, nitrofurantoin MR showed fewer patients with drug-related adverse events (5.6%) as judged by the investigator, compared to co-trimoxazole (9.4%) or trimethoprim (7.3%)(Figure 3).

Conclusion

Urinary tract infections are very frequent bacterial infection in women, with most cases being acute uncomplicated UTIs. Older patients with renal impairment have been found to have an increased risk of UTI-related hospitalisation and death. Nitrofurantoin is an antibiotic medication that is used for the treatment of uncomplicated lower UTI. It is effective against most Gram-positive and Gram-negative pathogens. Several major guidelines have declared nitrofurantoin as the first-line therapy for the treatment of uncomplicated lower UTIs. Of late, it has been shown that older adults with impaired kidney function who are treated with nitrofurantoin may not be at greater risk of an adverse outcome and are less likely to experience a hospital admission for worsening kidney function. Therefore, nitrofurantoin prescription can be used in selected patients with moderate-severe renal impairment.

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