

A matter of urgency: a brief update on the aetiology and treatment of uncomplicated urinary tract infections

SJ Brand

Department of Pharmacology, Faculty of Health Sciences, University of Pretoria, South Africa

Corresponding author, email: sarel.brand@up.ac.za

Health professionals in general practice regularly encounter women suffering from symptoms associated with urinary tract infections (UTIs). Uncomplicated UTIs have a high incidence and are commonly associated with recurrence. The widespread use of antimicrobials to treat community-acquired infections has resulted in the emergence of antimicrobial resistance. A rational approach to the pharmacotherapy of UTIs should therefore be followed and non-antimicrobial interventions be considered where possible.

Keywords: antimicrobial, cystitis, pyelonephritis, resistance, urinary tract infection

Introduction

The urethra, dedicated to the expulsion of urine, also provides passage to pathogens into the urinary tract. Contrary to conservative belief, urine is not sterile but may contain resident bacterial communities or urinary microbiota.^{1,2} These are believed to be distinct from those bacteria that lead to clinical urinary tract infections (UTIs)^{1,3} and the presence of bacteria should therefore not be considered a tell-tale sign of infection.⁴ It has even been suggested that UTIs may represent a state of dysbiosis of the urinary microbiota rather than the presence of a pathogenic species.^{5,6}

Bacteria routinely occur around the opening of the urinary tract from where they may colonise the urethra but are cleared during micturition.^{7,8} For UTIs to develop, the offending organism needs to be able to grow in urine and enter the urethra either via the urine or by ascending along the mucosal tissue. In females, large periurethral bacterial colonies occur in the regions surrounding the rectum and vagina.⁷ Additionally, commensal *Lactobacillus sp.* which usually protects against pathogens, is sensitive to vaginal pH – a parameter that is altered in postmenopausal women due to decreases in oestrogen.⁹ These factors, combined with the short distance from the urethral opening to the bladder, leave women – postmenopausal women in particular – at risk of developing UTIs more frequently.⁸ Other risk factors for developing a UTI include sexual intercourse, previous UTIs, a family history of UTI, the use of spermicides, and the introduction of a new sexual partner.¹⁰

The rate of incidence of UTIs is highest among women between the ages of 15 and 29 years (approximately 20%), and may be partly attributed to the increased likelihood of individuals being involved in sexual activity during this stage of their lives.⁸

Aetiology and diagnosis

The most common uropathogen is *Escherichia coli* (UPEC) with an incidence of at least 75% (up to 90%), while *Proteus mirabilis*, *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Streptococcus agalactiae*, and *Enterobacter* species may also be

involved in uncomplicated UTIs.^{11,12} Interestingly, more than a fifth of patients who present with symptoms associated with cystitis have negative urine cultures.^{8,13} Culturing methods optimised to detect commonly occurring, fast-growing uropathogens like UPEC and minimum thresholds that are applied when quantifying cultures have been presented as possible explanations for this.^{14,15} However, all patients presenting with symptoms typically associated with UTIs respond to appropriate antimicrobial treatment.¹⁵

UTIs are classified according to their anatomical presentation and may either occur in the lower, i.e. cystitis, or the upper, i.e. pyelonephritis, urinary tract and either be classified as complicated or uncomplicated. Complicated UTIs may be more difficult to diagnose and treat and are often associated with antimicrobial resistance. These include infections at the extremes of ages, male patients, pregnant women, and those associated with catheterisation. Considering its frequent presentation in general practice, this review focuses on uncomplicated UTIs.

Physical examination and patient history (Table I) serve as the most valuable screening tools when diagnosing UTIs. Evidence of pyuria and/or bacteriuria, i.e. the presence of leukocytes and/or bacteria in the urine, may be acquired via microscopy or a dipstick-based urinalysis and urine culture. While the cost and labour associated with these additional measures limit their routine use,¹⁴ most cases of uncomplicated cystitis do not require culturing and laboratory confirmation in patients who are otherwise considered to be healthy. This notion is supported by evidence that females presenting with two or more symptoms associated with UTIs have a probability of at least 90% to suffer from cystitis.¹⁶ However, urine culture is encouraged in cases of suspected pyelonephritis to establish antimicrobial sensitivity of the pathogen.^{11,15} It may also be considered when urethritis, cervicitis, vaginitis (all associated with dysuria) or a sexually transmitted infection is suspected¹⁷ or in patients suffering from recurrent UTI.¹¹ Aside from a delayed discovery of complicating factors, it is rarely recommended to perform urine cultures after successful antimicrobial treatment.¹⁸

Table I: Clinical presentation of patients with uncomplicated UTIs¹⁵

Cystitis	
• dysuria with or without	
▫ frequency	
▫ urgency	
▫ suprapubic pain	
▫ haematuria	
Pyelonephritis	
• fever (> 38 °C)	
• chills	
• flank pain	
• costovertebral-angle tenderness	
• nausea and/or vomiting	
• any of the above with or without	
▫ symptoms associated with cystitis	

Treatment

Uncomplicated cystitis is considered to be relatively harmless and does not often progress to pyelonephritis, even in patients who do not receive antimicrobial therapy.¹⁵ Considering the increasing prevalence of antimicrobial resistance, it may be of value to consider strategies that focus on symptomatic treatment and delayed antimicrobial treatment. Unfortunately, these alternative approaches are uncommon in clinical practice. The main reason for this is probably related to the significant morbidity associated with UTIs.¹⁵ As a result, antimicrobial agents are routinely prescribed to expedite recovery. Furthermore, due to its high incidence and propensity for recurrence in both cystitis (25% of women within six months¹⁹) and pyelonephritis, UTIs present a significant economic burden to the healthcare system.

The selection of first-line therapy should be based on several factors, including cost, patient compliance, possible drug allergies, potential side-effects, and, importantly, microbial susceptibility.¹² Some antimicrobials also have a greater potential for inducing so-called ecological adverse effects, i.e. promoting antibacterial resistance.²⁰

First-line therapy for uncomplicated cystitis includes either nitrofurantoin or fosfomycin (Table II). Nitrofurantoin is well absorbed and rapidly cleared from systemic circulation. It has activity against both Gram-positive and Gram-negative

organisms, inhibiting bacterial protein synthesis by several mechanisms, and acts as a bactericidal at the concentrations reached in the bladder.^{21,22} With little tissue penetration and high concentration in the urine, its antimicrobial activity is therefore largely focused on the bladder. It is important to note that its action is pH-dependent and is largely inhibited by the co-administration of urinary alkalinisers. While it is not active against *P. aeruginosa*, some *Klebsiella* strains, and *Proteus sp.*, resistance in *E.coli* is very uncommon and slow to develop.²¹ Fosfomycin, excreted via the kidneys and concentrating in the urine, also has broad antibacterial activity, is dependent on a low pH environment, and acts by inhibiting cell wall synthesis. It is highly active against *E. coli*^{20,23} while *S. saprophyticus*, *Klebsiella*, and *Enterobacter sp.* display varying levels of susceptibility.²⁴

While some guidelines also suggest the use of amoxicillin and trimethoprim-sulfamethoxazole,²⁵ South African data suggests a high incidence of antibiotic resistance associated with the use thereof. As such, it should not be included in the empirical treatment of UTIs.^{20,23,26} When combined with clavulanic acid, however, amoxicillin has a susceptibility profile similar to cephalosporins.^{12,26} While ciprofloxacin is suggested as first-line therapy by the South African Antibiotic Stewardship Programme,²⁷ it is well-known for its ecological adverse effects which have translated to rising levels of resistance against this fluoroquinolone antibiotic.^{12,23,26} Resistance most often occurs in *E. coli*, *Enterobacter*, and *Klebsiella* which are all implicated in UTI.²⁸ Accordingly, it is suggested that the use of ciprofloxacin be reserved^{15,25} or even excluded from empirical therapy.²⁰ However, when prescribed, patients should be monitored closely for relapse and urine samples submitted for culturing in cases where relapse does occur.²⁶

While most cases of uncomplicated acute pyelonephritis can successfully be treated on an outpatient basis, admission and parenteral therapy may be necessary in severe cases or in the presence of complicating factors, e.g. diabetes or pregnancy.¹⁵ Inpatients are treated intravenously with an aminoglycoside, a cephalosporin, or carbapenem based on local resistance data (Table III).¹¹ When moving to an outpatient setting, treatment is de-escalated to narrower-spectrum antibiotics.^{11,26} While fluoroquinolones are the drug of choice for empirical treatment of uncomplicated pyelonephritis, treatment should be

Table II: Guidelines for empirical treatment of uncomplicated cystitis^{15,26}

Drug choice	Dosage	Comment
First-line therapy		
Nitrofurantoin (at least 5 days)	100 mg TID (with meals)	Minimal ecological adverse effects. Avoid if pyelonephritis suspected.
Fosfomycin	3 g stat	
Second-line therapy		
Fluoroquinolones (at least 3 days):		High potential for ecological adverse effects; reserve use where possible. Newer quinolones, e.g. moxifloxacin achieve insufficient urinary concentration.
Ciprofloxacin	250 or 500 mg BD	
Levofloxacin	250 or 500 mg OD	
Beta-lactams (at least 5 days):		Amoxicillin has reduced microbial susceptibility. Relatively few ecological adverse effects compared to parenteral preparations.
Amoxicillin-clavulanate	250 or 500/125 mg TID	
Third-generation cephalosporins		
Cefixime	200 mg BD	
Cefpodoxime	100 mg BD	

Table III: Guidelines for empirical treatment of uncomplicated pyelonephritis^{15,26}

Drug choice	Dosage	Comment
Oral therapy		
Fluoroquinolone agents (7 days): Ciprofloxacin Levofloxacin	500 mg BD 750 mg OD	Potential for ecological adverse effects; reserve use until susceptibility results available.
Trimethoprim-sulfamethoxazole (14 days)	160/800 mg BD	Fewer ecological adverse effects compared to fluoroquinolones
Beta-lactam agents (10–14 days): Amoxicillin-clavulanate Third-generation cephalosporins Cefixime Cefpodoxime	875/125 mg BD 200 mg BD 100 mg BD	Amoxicillin has reduced microbial susceptibility. Relatively few ecological adverse effects compared to parenteral preparations.
Intravenous therapy		
Amikacin Ceftriaxone Ertapenem	15 mg/kg OD 1 g IV OD 1 g IV OD	Hospitalisation and parenteral treatment recommended for severe infections and pregnant patients.

guided by the susceptibility of the causative organism.^{15,26} Fluoroquinolones act by blocking bacterial DNA synthesis via inhibition of bacterial topoisomerase II and IV. Ciprofloxacin and levofloxacin have excellent Gram-negative activity and good activity against Gram-positive bacteria.²⁸

Recurrent UTI occurs in up to 10% of female patients and may be due to re-infection, i.e. more than two weeks after successful treatment, or relapse, i.e. within two weeks of initial treatment with the same organism; usually due to antimicrobial resistance.^{15,26} Prophylactic antimicrobial treatment significantly reduces the recurrence of cystitis¹⁵ but prophylactic use of trimethoprim-sulfamethoxazole for UTIs and *Pneumocystis jirovecii* in immunocompromised patients has contributed to bacterial resistance.²⁰ As such, nitrofurantoin 100 mg or cephalexin 250 mg is suggested for either post-coital prophylaxis (as a single dose) or for continuous daily prophylaxis (once daily up to two years) in patients who have had three or more UTIs in the past 12 months or two or more UTIs in the past six months. In such cases, at least one previous infection should have been confirmed with a positive culture and non-antimicrobial approaches should have been considered.¹⁵

Non-antimicrobial approaches

Considering that sexual intercourse and personal hygiene are major contributors to the prevalence of uncomplicated cystitis, several precautions can be taken to mitigate the risk thereof and patient counselling should be prioritised – with or without antimicrobial treatment. Decreasing the frequency of sexual intercourse may not always be a rational expectation, but limiting this to one sexual partner may be of value. Additionally, the use of spermicides and/or condoms coated with spermicides could be substituted with oral contraception and/or uncoated condoms to negate the unfavourable effects thereof on the microbiota. Patients should also urinate after intercourse and wipe from front to back after defecation.

Proanthocyanidins, that occur naturally in cranberry juice, have been claimed to reduce bacterial adherence to uroepithelial cells and thereby decrease the risk of developing UTIs. However,

several randomised, placebo-controlled clinical trials have delivered conflicting evidence on both the purported protective effect of cranberry juice and its efficacy in reducing the risk of recurrent UTI.²⁹⁻³¹

D-Mannose has been demonstrated to inhibit bacterial adhesion to uroplakin receptors on uroepithelial cells by saturating FimH adhesin in enteric bacteria.³² While research is ongoing, several findings support its usefulness in preventing UTIs.^{33,34} The protective role of an intact microbiome has also gained traction in the prevention of recurrent UTIs. While probiotic (*Lactobacillus*) therapy has been demonstrated to be beneficial in several placebo-controlled studies, large-scale clinical data is still lacking.

Summary

Uncomplicated UTIs, while mostly benign, are associated with high prevalence and morbidity and are recurrent in a large proportion of female patients. Due to the increasing incidence of antibacterial resistance, non-antimicrobial approaches (including symptomatic treatment) should be considered and patient counselling prioritised. Should these approaches fail, guidelines for the use of antimicrobial agents provide an effective route to eradicate the offending uropathogen.

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